ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2022, Volume 11, Number 3: 1865-1869
P-ISSN.2089-1180, E-ISSN: 2302-2914

The relationship between inflammatory markers and vitamin D levels with the severity of coronary artery disease in elderly patients

Charles Limantoro[1*], Fandy Santoso[1], Catharina Suharti[2], Trilaksana Nugroho[3]

[1]Division of Cardiology, Departement of Internal Medicine, Faculty of Medicine, Universitas Diponegoro – Dr. Kariadi General Hospital, Semarang, Indonesia; [2]Division of Hematology and Oncology Medic, Departement of Internal Medicine, Faculty of Medicine, Universitas Diponegoro – Dr. Kariadi General Hospital, Semarang, Indonesia; [3]Departement of Ophtamology, Faculty of Medicine, Universitas Diponegoro – Dr. Kariadi General Hospital, Semarang, Indonesia;

*Corresponding author:
Charles Limantoro;
Division of Cardiology, Departement of Internal Medicine, Faculty of Medicine, Universitas Diponegoro – Dr. Kariadi General Hospital, Semarang, Indonesia;
c_limantoro@yahoo.com

Received: 2022-08-08
Accepted: 2022-11-04
Published: 2022-12-01

ABSTRACT

Introduction: Coronary artery disease (CAD) is the accumulation of atherosclerotic plaques in the coronary arteries. CAD is the most common cause of death worldwide, and its prevalence continues to increase, especially in the elderly population. Atherosclerosis is a chronic inflammatory condition that involves various inflammatory markers, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In the inflammatory process, vitamin D plays an essential role in developing atherosclerotic plaques affecting the severity of CAD. The elderly are susceptible to vitamin D deficiency and an increase in the inflammatory process related to the severity of CAD. Therefore, this study aims to prove the relationship between inflammatory markers and vitamin D levels with the severity of CAD in elderly patients.

Methods: This study used a cross-sectional design in stable CAD patients aged 60 - 75 years who had passed through coronary arteriography. The severity was assessed from the angiography results using the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, which 3 cardiovascular consultants evaluated and the average outcome was calculated. TNF-α, IL-6, and vitamin D were taken during angiography and examined using high sensitivity enzyme-linked immunoabsorbent assay (ELISA). The correlation test was analyzed using Spearman's Rank correlation test.

Results: A total of 38 subjects were included in this study, where 30 (78.9%) patients were male. The mean age of the patients was 64.79 years, and the prevalence of vitamin D deficiency was 57.9%. There was a moderately significant positive correlation between markers of inflammation TNF-α (r=0.499, p=0.001) and IL-6 (r=0.518, p=0.001) and the SYNTAX score. A weak negative correlation was also discovered between vitamin D and the SYNTAX score (r=-0.335, p=0.040).

Conclusion: The levels of inflammatory markers (TNF-α and IL-6) and vitamin D correlated with the severity of CAD in elderly patients.

Keywords: Coronary artery disease, elderly, TNF- α, IL-6, vitamin D, SYNTAX score.
Cite This Article: Limantoro, C., Santoso, F., Suharti, C., Nugroho, T. 2022. The relationship between inflammatory markers and vitamin D levels with the severity of coronary artery disease in elderly patients. *Bali Medical Journal* 11(3): 1865-1869. DOI: 10.15562/bmj.v11i3.3631

INTRODUCTION

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the coronary arteries.[1–3] CAD is the most common cardiovascular disease and one of the leading causes of death worldwide, including in Indonesia. The prevalence of the disease increases with age in both men and women, where the elderly population is the most vulnerable group.[2,3]

Atherosclerosis is a chronic inflammatory state involving various markers, including various inflammatory cytokines. According to previous studies, the roles of pro-atherogenic inflammatory cytokines include tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In the elderly population, it is suspected that there is an increase in the activation of the inflammatory system.[2–4]

Vitamin D is widely known for its function in calcium homeostasis and bone formation. It also plays a role in the inflammatory process and the immune system, which affects the formation and development of atherosclerotic plaques.[5] Deficiency of vitamin D is a global pandemic in Indonesia, especially among the elderly population and is thought to play a role in the severity of CAD in the elderly.[6,7]

There are conflicting results on the correlation between inflammatory markers and vitamin D levels with the severity of CAD using various examination methods.[8–14] Therefore, this study aims to prove the relationship between inflammatory markers and vitamin D levels with the severity of CAD in elderly patients. Previous reports on the relationship between serum vitamin D levels and inflammatory markers were assessed from TNF-α and IL-6 with the severity of CAD using the SYNTAX score, specifically in the elderly group, based on observations. This study is expected to provide additional knowledge for the proper and holistic management of CAD patients in Indonesia, especially the elderly.

MATERIAL AND METHODS

The cross-sectional design was carried out on 38 stable CAD patients aged 60-75 years who had passed through

coronary angiography in the cardiac catheterization laboratory of Dr. Kariadi Hospital Semarang. The selection of elderly subjects is limited to 60-75 years according to the WHO classification of the "elderly" age group. This study was carried out from February to July 2021 using the consecutive sampling method.

Patients with the acute coronary syndrome, acute heart failure, active infection, history of autoimmune disease, malignancy, grade IV–V chronic renal failure, clinical chronic liver disease, acute stroke, previous coronary intervention, history of vitamin D supplementation, and long-term use of anti-inflammatory drugs length (>1 month) were excluded from the study.

The objectives, benefits, and procedures were explained directly and in writing to all subjects, and each agreed by signing informed consent. This study received ethical clearance with code number 695/EC/KEPK-RSDK/2020 from the Health Research Ethics Committee of Dr. Kariadi Hospital Semarang.

Inflammation markers and vitamin D

The samples were taken from the patient's arterial blood during coronary angiography, performed, and stored in aliquots frozen in a freezer at -80 degrees Celsius. Subsequently, the samples were collected, and aliquots were sent to examine inflammatory markers (TNF-α and IL-6), and vitamin D levels together with the ELISA method. The results were read with an ELX 800 microplate reader (BioTek Instruments, Inc.) at a wavelength of 400 nm in an accredited GAKI laboratory, Faculty of Medicine, Diponegoro University (UNDIP).

Severity of CAD

Coronary arteriography examination is the standard method for diagnosing CAD and can be used to assess its severity. The coronary arteriographic severity was assessed using the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score. The SYNTAX score is a semi-quantitative method to examine the severity of CAD from coronary angiographic images based on the complexity, location, and the number of lesions.[15,16] Therefore, the higher the SYNTAX score, the more severe CAD and vice versa. Three cardiovascular consultants assessed the SYNTAX score, and the results were averaged.

Statistical analysis

The data was processed and analyzed using SPSS software version 16.00 for Windows. The results of the TNF-α, IL-6, vitamin D, and SYNTAX scores were presented in numerical data. Subsequently, univariate analysis was conducted to describe the characteristics of the subjects in descriptive statistics and presented in tabular form. Bivariate analysis was also conducted to determine the relationship between the independent and the dependent variables. The Mann-Whitney and Kruskal Wallis tests were used to examine the relationship between the confounding variables and the SYNTAX score. The normality test of the data with the Shapiro-Wilk test showed that the data distribution for the independent and the dependent variables was not normal. The correlation test between inflammatory markers and vitamin D with the SYNTAX score was analyzed using the Spearman's Rank correlation test. This is because the data distribution was not normal; moreover, there was a statistically significant correlation when p≤ 0.05. Multivariate analysis was performed with a multiple linear regression test on the independent variables with a SYNTAX score.

RESULTS

The 38 subjects who met the inclusion criteria comprised 30 (78.9%) males and 8 (21.11%) females with a median age of 64.5 years. The highest risk factors for CAD consisted of 31 (81.6%) hypertension, 31 (81.6%) dyslipidemia, and 21 (55.3%) smoking history. The most used drugs were 32 (84.2) statin groups, 29 (76.3%) salicylic acid, and 26 (68.4%) angiotensin-converting enzyme (ACE-i) inhibitors. The inflammatory marker levels assessed included TNF- levels were found to be increased in 15 (39.5%) subjects with a median of 4.7 (0.1-19.6) pg/mL and IL-6 levels in 25 (65, 8%) subjects with 4.62 (0.12-25.42) pg/mL.

Vitamin D levels were higher in 22 (57.9%) subjects with insufficient status compared to 16 (42.2%) sufficient subjects with a median of 28.5 (13-69) ng/mL. Meanwhile, there were no subjects with vitamin D deficiency status. SYNTAX score assessment obtained a median of 17

Table 1. Characteristics of subjects.

Variable	Values
Gender (male), n (%)	30 (78.9)
Age (years), median (RIK)	64.5 (60 – 75)
Risk factor, n (%)	
Obesity	13 (42)
Smoke	
Not a smoker	12 (31.6)
Former smoker	21 (55.3)
Smoker	5 (13.2)
Diabetes mellitus	11 (28.9)
Hypertension	31 (81.6)
Dyslipidemia	31 (81.6)
CKD-EPI (mL/min/1.73m2), median (RIK)	61.8 (34 – 103)
Drug use, n (%)	
ACE-i	26 (68.4)
Angiotensin receptor blockers (ARB)	9 (23.7)
Calcium channel blockers (CCB)	18 (47.4)
Statins	32 (84.2)
Aspirin	29 (76.3)
Clopidogrel	16 (42.1)
TNF-α (pg/mL), median (RIK)	4.7 (0.1 – 19.6)
IL-6 (pg/mL), median (RIK)	4.62 (0.12 – 25.42)
Vitamin D (ng/mL), median (RIK)	28.5 (13 – 69)
SYNTAX score, median (RIK)	17 (6 – 39.5)

Table 2. Tests of confounding variables on the SYNTAX score.

Variable	SYNTAX Score	p
Gender		
Male	18.5 (6 - 39.5)	0.361‡
Female	10.5 (6 - 39.5)	
Risk Factors		
Obesity		
Yes	11 (7 - 38.5)	0.218‡
No	19.5 (6 - 39.5)	
Diabetes mellitus		
Yes	21 (7 - 38.5)	0.499‡
No	16 (6 - 39.5)	
Hypertension		
Yes	16 (6 - 39.5)	0.749‡
No	18 (6 - 39.5)	
Dyslipidemia		
Yes	19.5 (6 - 39.5)	0.181‡
No	10 (6 - 39.5)	
Smoke		
Not a smoker	11 (6 - 39.5)	0.371¶
Former smoker	18 (6 - 38.5)	
Smoker	19.5 (6 - 39.5)	
Drug use		
ACE-i		
Yes	20.25 (6 - 39.5)	0.064‡
No	9.75 (6 - 38.5)	
ARB		
Yes	10.5 (8 - 31)	0.122‡
No	19.5 (6 - 39.5)	
CCB		
Yes	20.25 (6 - 35.5)	0.539‡
No	15.5 (6 - 39.5)	
statins		
Yes	19.25 (6 - 39.5)	0.155‡
No	10.5 (6 - 24)	
Aspirin		
Yes	19 (6 - 39.5)	0.344‡
No	12 (6 - 39.5)	
Clopidogrel		
Yes	20.25 (6 - 38.5)	0.351‡
No	14 (6 - 39.5)	

Notes: ‡Mann Whitney test; ¶Kruskal Wallis Test

Table 3. Correlation test of the independent variables on the SYNTAX score.

Variable	SYNTAX Score	
	r	p
Age	-0.02	0.886§
CKD-EPI	-0.14	0.247§
TNF-α	0.499	0.001§
IL-6	0.518	0.001§
Vitamin D	-0.335	0.040§

Note: §Spearman's rank Correlation Test

with the lowest highest scores of 6 and 39, respectively, as shown in table 1.

The results of the bivariate analysis of different tests in table 2 showed no difference between risk factors for CAD (confounding variables) and drug use with a SYNTAX score.

There is a moderately significant positive correlation between levels of TNF-α, IL-6, and SYNTAX scores (r=0.499, r=0.518, p=0.001, p=0.001, sequential). Spearman's rank correlation test between vitamin D levels and the SYNTAX score discovered a negative correlation with a significant weak strength (r=-0.335, p=0.040) as shown in table 3.

Multivariate analysis with multiple linear regression was performed on the independent variable on the SYNTAX score. The results showed that the level of IL-6 is a variable that has a significant effect ($p < 0.001$) on the SYNTAX score.

DISCUSSION

CAD remains a global health threat, including in Indonesia. Meanwhile, identifying its severity predictors is very helpful in management efforts in prevention, diagnosis, and therapy.

The majority of the subject's gender was male (78.9%); this is consistent with the classic risk factors of CAD being more dominant in males. The mean age of the patients in this study was 64.79 ± 4.32 years. The subject criteria used were CAD patients aged between 60-75 years. The risk of developing CAD increases with age and the elderly population is the most vulnerable.[17]

Epidemiological studies of vitamin D deficiency prevalence in America, Europe, the Middle East, and Asia are around 30-50%.[18] A report from Southeast Asia conducted by SEANUT in 2016 discovered that the prevalence of vitamin D deficiency was around 45%.[19] In this study, the prevalence of vitamin D insufficiency was 57.9%; although there were no patients with vitamin D deficiency status, the prevalence of vitamin D insufficiency was higher than sufficient. This is because the subjects were the elderly population more susceptible to vitamin D deficiency and increasing age is a risk factor for the prevalence.

Inflammatory markers in the form of inflammatory cytokines are "messengers" of inflammation and the immune system that play a role in every stage of atherosclerotic plaque formation. Although risk factors for the development of atherosclerosis have been well identified, the response to inflammatory markers is also important to determine the risk of developing CAD, especially in the elderly population.[20] The examination of inflammatory cytokines indicated the levels of TNF-α and IL-6, which are

cytokines pro-inflammatory.[3] The results showed that TNF-α levels were positively correlated with moderate strength (r=0.499, p=0.001) with SYNTAX score. Similarly, IL-6 levels (r=0.518, p=0.001) were also positively correlated with moderate strength with SYNTAX score, which is statistically significant. A positive correlation was found in the relationship between TNF-α and SYNTAX score as well as the relationship between IL-6 and SYNTAX scores. This indicated that the higher the TNF-α or IL-6 levels, the higher the SYNTAX score, showing the severity of CAD in the elderly.

These results align with Gostman I., et al. who determined the association between levels of various inflammatory markers and angiographic CAD severity in 201 patients. These include patients who have passed through coronary angiography in cases of stable CAD and developed ACS within 6 months.[20] Min X et al. also examined various inflammatory cytokines including TNF-α and IL-6 levels on the severity of CAD assessed by the Gensini score in 201 patients who had coronary angiography with complaints of chest pain. It was discovered that TNF-α levels had a weak positive correlation (r=0.303) and IL-6 levels (r=0.511) had a moderately positive correlation with the severity of CAD as assessed by a statistically significant Gensini score (p<0.01).[21]

The relationship between inflammatory markers (TNF- α and IL-6) with the severity of CAD in the elderly has occurred in several mechanisms. These include high oxidative stress, namely an increase in reactive oxygen species and a decrease in nitric oxide which causes endothelial dysfunction, high oxidized LDL, and an increase in megakaryopoiesis leading to the release of young platelets with a larger volume. Therefore, platelets tend to be more active.[22,23] Another mechanism is high endothelial cell activation, namely an increase in the expression of adhesion molecules such as E-selectin, vascular cell adhesion molecule (VCAM) -1, and intercellular adhesion molecule (ICAM)-1. There is an increase in the recruitment of leukocytes through nuclear factor kappa beta (NFkB)[24], as well as high stimulation and migration of smooth muscle cells in the tunica media to the tunica intima, which leads to a more complex atherosclerotic plaque.[25–28] The inflammatory process also increases in the elderly.[22]

Exploration of vitamin D's role outside the bone is assumed to influence the formation and development of atherosclerotic plaques that affect the severity of CAD. This is because vitamin D receptors are also found in the cardiovascular system.[5] In this study, it was discovered that vitamin D levels had a weak negative correlation with the SYNTAX score (r=-0.355), which was statistically significant (p=0.040). The negative correlation with the SYNTAX score indicates that the lower the vitamin D level, the higher the SYNTAX score; therefore, CAD becomes more severe among the elderly.

The results are in line with Akin F, et al. which is the first study to assess the relationship between vitamin D levels and the severity of CAD using coronary angiography for examination with the Gensini score. Meanwhile, Akin F, et al. discovered that vitamin D levels had a moderate negative correlation, which was statistically significant (r=-0.416, p<0.001) with the Gensini score describing the severity of CAD and this correlation.[8] These values are the same as previous studies with a larger number of subjects such as Verdoia M, et al. on 1484 subjects. In this study, the assessment of the severity of CAD is said to be severe when it involves the left main and or 3 coronary arteries. Verdoia M, et al. discovered that vitamin D deficiency was significantly associated with the prevalence of CAD (OR=1.32(1.1-1.6), p=0.0004) and CAD with higher severity (OR=1.18(1-1.39), p=0.05).[9]

The relationship between vitamin D in influencing the severity of CAD is assumed to be through the correlation with various cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, heart function, and inhibition of the synthesis of vascular endothelial growth factors (VEGF). This also includes its effect on inflammation, namely vitamin D as an anti-lymphoproliferative that inhibits the differentiation of monocytes into macrophages, thereby limiting various inflammatory cytokines produced, including TNF-α, and IL-6.[29,30]

The limitations of this study were, firstly, it involved only 2 types of inflammatory cytokines examined as markers of inflammation. In contrast, other types can also be associated with the severity of CAD in the elderly. Secondly, the use of a cross-sectional design, where measurements of inflammatory markers and vitamin D were carried out once. This makes it difficult to determine lifetime level as atherosclerosis continues and affects the degree severity of CAD. Therefore, further study is suggested to involve more inflammatory markers. Prospective investigation can also be carried out to understand better the relationship and efficacy of vitamin D levels and inflammatory markers on the severity of CAD. At the same time, experimental studies of vitamin D supplementation are also recommended to determine its effect on inflammatory markers and the severity of CAD.

CONCLUSION

The inflammatory markers (TNF-α and IL-6) and vitamin D levels correlated with the severity of CAD in elderly patients.

ACKNOWLEDGMENTS

None.

DISCLOSURE

The author reports no conflicts of interest in this work.

FUNDING

None.

AUTHOR CONTRIBUTION

CL contributed in concepts, design, definition of intellectual content, literature search, manuscript review, and guarantor. FS contributed in literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. CS contributed in concepts, design, definition of intellectual content, literature search, and manuscript review. TN contributed in literature search, data acquisition, data analysis, statistical analysis, and manuscript review.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;41(3):407–77. Available from: https://doi.org/10.1093/eurheartj/ehz425
2. Gregersen I. Inflammatory Mechanisms in Atherosclerosis. In: Gianturco BHE-L, editor. Rijeka: IntechOpen; 2018. p. 31–45. Available from: 10.5772/intechopen.72222
3. Tousoulis D, Oikonomou E, Economou EK, Crea F, Kaski JC. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. *Eur Heart J*. 2016;37(22):1723–32. Available from: 10.1093/eurheartj/ehv759
4. Ismail D, Purwanto B, Wasita B, Supomo, Yasa KP, Soetrisno. Exploring the role of the combination of propolis and vitamin D3 on VCAM-1 and Caspase-3 expression in preventing atherosclerosis in chronic kidney disease rats. *Bali Med J*. 2022;11(1 SE-ORIGINAL ARTICLE):160–5. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/3194
5. Aggarwal R, Akhthar T, Jain SK. Coronary artery disease and its association with Vitamin D deficiency. *J Midlife Health*. 2016;7(2):56–60. Available from: 10.4103/0976-7800.185334
6. Milazzo V, De Metrio M, Cosentino N, Marenzi G, Tremoli E. Vitamin D and acute myocardial infarction. *World J Cardiol*. 2017;9(1):14–20. Available from: 10.4330/wjc.v9.i1.14
7. Limantoro C, Catharina Suharti, Trilaksana Nugroho, Friska Wilda Wijaya. Relationship between Vitamin D Levels and Platelet Function in the Elderly Patients with Coronary Heart Disease. *Bali Med J*. 2022;11(3 SE-ORIGINAL ARTICLE):1594–7. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/3911
8. Akin F, Ayça B, Köse N, Duran M, Sarı M, Uysal OK, et al. Serum Vitamin D Levels Are Independently Associated With Severity of Coronary Artery Disease. *J Investig Med*. 2012;60(6):869 LP – 873. Available from: 10.2310/JIM.0b013e31825457cb
9. Verdoia M, Schaffer A, Sartori C, Barbieri L, Cassetti E, Marino P, et al. Vitamin D deficiency is independently associated with the extent of coronary artery disease. *Eur J Clin Invest*. 2014;44(7):634–42. Available from: 10.1111/eci.12281
10. Moradi M FA. Evaluation of vitamin D levels in relation to coronary CT angiographic findings in an Iranian population. *Vasc Heal Risk Manag*. 2017;13:361–7. Available from: https://doi.org/10.2147/VHRM.S142721
11. Muvva Venkateswarlu K, Durgaprasad R, Sachan A, Pathakota SR, Narendra CH, Kanavath SN. Correlation of plasma 25-hydroxy-vitamin D level with angiographic severity in coronary artery disease. *J Indian Coll Cardiol*. 2018;8(2):57–60. Available from: https://doi.org/10.1016/j.jicc.2018.02.001
12. Rahman A, Karmakar P, Jabeen S, Nabi S, Khan A, Shahriar MS, et al. Association of Vitamin D Level with Severity of Angiographically Documented Coronary Artery Disease: Observations from Bangladeshi Patients. *J Cardiovasc Dis Res*. 2019;10:52–7. Available from: 10.5530/jcdr.2019.2.10
13. Mustafa Umut Somuncu MD, Nail Güven Serbest, M.D., Ferit Akgül MD, Mustafa Ozan Çakır MD, Tunahan Akgün, M.D., Fatih Paşa Tatar MD, Murat Can, M.D., Abdulkadir Tekin MD. The relationship between a combination of vitamin D deficiency and hyperuricemia and the severity of coronary artery disease in myocardial infarction patients. *Turk Kardiyol Dern Ars 2020*. 2020;48(1):10–9. Available from: doi: 10.5543/tkda.2019.89743
14. Ali MH, Heba FT OF. Vitamin D Levels Assessment in Relation to Coronary MDCT Angiographic Findings. *ZUMJ*. 2020;26(1):53–63. Available from: doi: 10.21608/zumj.2019.16328.1470
15. Sianos G, Morel M-A, Kappetein AP, Morice M-C, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1(2):219–27. Available from: http://dx.doi.org/10.4244/eijv8i11a196
16. Morice M-C, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and. *Circulation*. 2010;121(24):2645–53. Available from: 10.1161/CIRCULATIONAHA.109.899211
17. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med*. 1976;85(4):447–52. Available from: 10.7326/0003-4819-85-4-447
18. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and Skin Physiology: A D-Lightful Story. *J Bone Miner Res*. 2007;22(S2):V28–33. Available from: 10.1359/jbmr.07s211
19. Poh BK, Rojroongwasinkul N, Nguyen BK Le, Sandjaja, Ruzita AT, Yamborisut U, et al. 25-hydroxy-vitamin D demography and the risk of vitamin D insufficiency in the South East Asian Nutrition Surveys (SEANUTS). *Asia Pac J Clin Nutr*. 2016;25(3):538–48. Available from: 10.6133/apjcn.092015.02
20. Gotsman I, Stabholz A, Planer D, Pugatsch T, Lapidus L, Novikov Y, et al. Serum cytokine tumor necrosis factor-alpha and interleukin-6 associated with the severity of coronary artery disease: indicators of an active inflammatory burden? *Isr Med Assoc J*. 2008;10(7):494–8. Available from: http://dx.doi.org/10.1902/jop.2007.060301
21. Min X, Lu M, Tu S, Wang X, Zhou C, Wang S, et al. Serum Cytokine Profile in Relation to the Severity of Coronary Artery Disease. *Biomed Res Int*. 2017;1–9. Available from: 10.1155/2017/4013685
22. Urschel K, Cicha I. TNF-α in the cardiovascular system: from physiology to therapy. *Int J Interf Cytokine Mediat Res*. 2015;7:9–25. Available from: https://doi.org/10.2147/IJICMR.S64894
23. Cure MC, Cure E, Yuce S, Karakoyun I, Efe H. Mean Platelet Volume and Vitamin D Level. *Ann Lab Med*. 2014;34(2):98–103. Available from: https://doi.org/10.3343/alm.2014.34.2.98
24. Rathored J, Sharma SK, Singh B, Banavaliker JN, Sreenivas V, Srivastava AK, et al. Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D. *Int J Tuberc Lung Dis*. 2012;16(11):1522–8. Available from: 10.5588/ijtld.12.0122
25. Wang H, Xia N, Yang Y, Peng D-Q. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids Health Dis*. 2012;11:42. Available from: 10.1186/1476-511X-11-42
26. Wung BS, Hsu MC, Wu CC, Hsieh CW. Resveratrol suppresses IL-6-induced ICAM-1 gene expression in endothelial cells: effects on the inhibition of STAT3 phosphorylation. *Life Sci*. 2005;78(4):389–97. Available from: 10.1016/j.lfs.2005.04.052
27. Finklea JD, Grossmann RE, Tangpricha V. Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies. *Adv Nutr*. 2011/04/30. 2011;2(3):244–53. Available from: 10.3945/an.111.000398
28. Ikeda U, Ikeda M, Oohara T, Oguchi A, Kamitani T, Tsuruya Y, et al. Interleukin 6 stimulates growth of vascular smooth muscle cells in a PDGF-dependent manner. *Am J Physiol*. 1991;260(5 Pt 2):H1713-7. Available from: 10.1152/ajpheart.1991.260.5.H1713
29. Martinesi M, Bruni S, Stio M, Treves C. 1,25-Dihydroxyvitamin D3 inhibits tumor necrosis factor-α-induced adhesion molecule expression in endothelial cells. *Cell Biol Int*. 2006;30(4):365–75. Available from: 10.1016/j.cellbi.2006.01.004
30. Oh J, Weng S, Felton SK, Bhandare S, Riek A, Butler B, et al. 1,25(OH)2 vitamin d inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. *Circulation*. 2009/08/10. 2009;120(8):687–98. Available from: 10.1161/CIRCULATIONAHA.109.856070