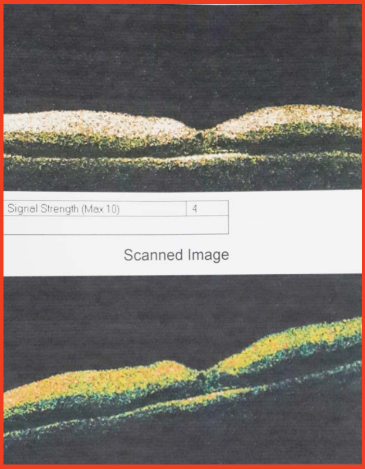
# INDONESIAN JOURNAL OF RHEUMATOLOGY

The official journal of Indonesian Rheumatology Association

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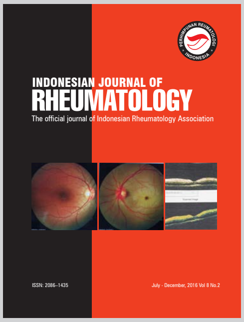


Cover image: A. Funduscopy result (left): normal eye; (right): central retinal artery occlusion shows cherry-red spot and pale retina. B. Optical Coherence Tomography (OCT) of the right eye: hyperreflective inner retinal layer.

**AIMS AND SCOPE**
*Indonesian Journal of Rheumatology* is self-focused on rheumatic diseases and connective tissue disorders in forms of original article (extended or concise reports), review articles, editorial, letters, leaders, lesson from memorable cases, book review, and matters arising. Both clinical and laboratory including animal studies are welcome.



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## Editorial



## Original article



## CASE REPORT



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# Editorial Note

YI Kasjmir

Rheumatic diseases spread around us. It is our responsibility to acknowledge them and giving an early intervention to prevent the disease progression that lead to patient's disability. In this edition, Indonesian Journal of Rheumatology will serve you with more varied topics, includes osteoporosis, rheumatoid arthritis, osteoarthritis, and systemic lupus erythematosus. We also shared an interesting case report about female patient with primary anti-phospholipid syndrome (APS) who came with manifestation on the left central retinal artery occlusion.[1] We hope the informations and knowledges that we shared may bring a new hope that could be used in your medical practices.

Osteoporosis is a pathological condition of the bones in the body. It is commonly occured in post-menopausal women and elderly. It usually comes with a mild symptoms and does not directly caused mortality and morbidity. However, it can be a commorbid disease of many diseases that could lead to disabilities and mortality. Thus early detection and intervention is needed. Making the diagnosis of osteoporosis, WHO recommends BMD measurement of the unilateral femur or hip. Unfortunately, some studies reported 30% patients showed a discordance BMD level of their hips which might lead to underdiagnose the osteoporosis disease. Therefore, a study by Widjanarko AL, et al. performed to assess whether we need to perform bilateral hip bone mineral density examination to made the diagnosis of osteoporosis.[2]

Unlike osteoporosis, rheumatoid arthritis is an autoimmune rheumatic disease with more obvious symptoms. It could lead to higher mortality and morbidity. Failed to control the disease activity might lead to severe disability in most patients. Adequate therapy is needed to control the disease activity, so the disease progression and complication could be avoided. To determine the disease activity, we usually use DAS28 as our modalities. DAS28 is applied widespread in clincal practices since the test is simple and easy to use. Realizing that the DAS28 has a limitation, since it is only assesing the symptoms of RA disease activity in the upper extremities, a modified DAS 28 was proposed, which is known as DAS28-squeeze. Besides the assesment of the 28 joints in the hand, DAS28-squeeze adding a MTP squeeze test. Since it haven't validated with other imaging modalities, Santosa D, et al. reported their study about the diagnostic value of DAS 28 and DAS 28-squeeze comparing with power doppler sonography as the reference standard.[3]

Higher mortality of RA patients usually related to atherosclerosis and cardiovascular diseases. The chronic inflammatory condition of RA causes a systemic inflamation that is related to the development of atherosclerosis and/or atherosclerotic plaques in the vascular system. Realizing that fact, Pambudi JR, et al. performed a study to assess any factors that could be used as a predictors of the development of atherosclerosis and atherosclerosis plaque.[4]

Besides the journals we stated above, in this volume, we also covered an interesting journal about the used of ultrasound to detect an early manifestation of osteoarthritis compared to standard X-ray that assessed with Kellgren-Lawrence (KL) score.[5] We also published three study about systemic lupus erythematosus (SLE), such as: Rifa'i A, et al. study about the effect of vitamin D supplementation on disease activity and fatique in SLE patients[6]; Praptama S, et al. study about correlation of 24-hour protein urine and eGFR in monitoring disease progression of nephritis lupus patients; and the last but not least, study by Anindito B, et al[7] about the validity and reliability of lupus quality of life questionaire in bahasa Indonesia to measure the quality of life in patients with SLE in Indonesia[8].

Finally, we are very pleased to invite all the reader to contribute in developing Indonesian Journals of Rheumatology by submitting your articles, in the field of original research, review paper, case report, letter to editor, and others form of scientific works. Please follow the instruction for author which is provided in our website (www.reumatologi.or.id), every articles will get a full consideration for the publication in Indonesian Journal of Rheumatology.

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## Interested to published your masterpiece?

We kindly invite you to contribute to Indonesian Journal of Rheumatology (IJR)

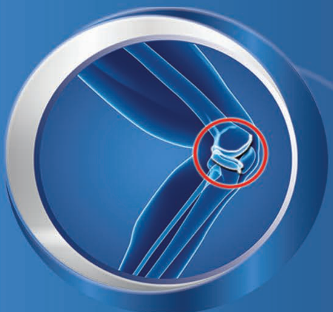
Please send your articles to our editorial team(pb.reumato@gmail.com). Every articles submitted to our journal will get a full consideration for publication. We accept all work related to rheumatology in the form of original articles, review articles, case reports, EBCRs, and etc.

Our Journals will be issued every 6 months.

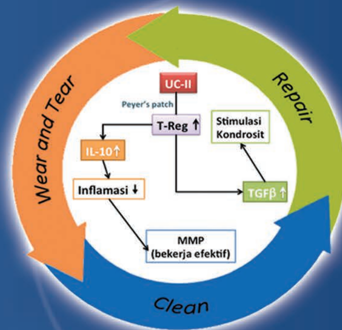
If you have any question, please do not hesitate to contact our staff by email or phone (editorial office), you can ask in English or Bahasa Indonesia.

Warm regards,

Editorial Team



## Advanced Choice for Joint Health




- UC-II melekat ke Peyer's Patch dan menstimulasi T-Reg.
- T–Reg menstimulasi Interleukin–10 (IL-10) dan Transforming Growth Factor–ß (TGF–ß).
- IL–10 membantu proses *clean* bekerja lebih baik
- TGF–ß menstimulasi kondrosit agar tubuh membentuk matrix tulang rawan, Proteoglikan dan Kolagen tipe 2.

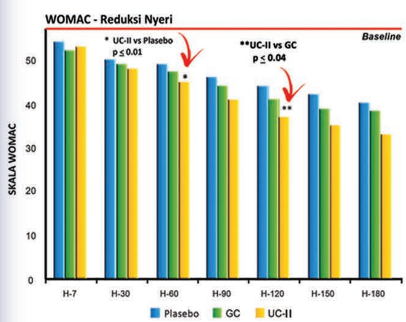
**UC-II adalah Collagen Type-II, berasal dari *Chicken Sternum Cartilage* yang diproses secara khusus (*undenaturated*), untuk memelihara kesehatan persendian.**

Lugo et al. Nutr J. 2016; 15:14

### Journal highlight

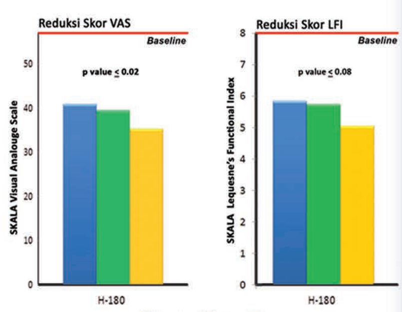
Metode Penelitian: *Randomized, Double-Blind,* N : 191 Pasien terbagi dalam 3 group, penerima dosis UC II 40 mg, Glucosamine 1.500 mg dan Chondroitin 1.200 mg dan Plasebo.

**UC-II lebih efektif mengurangi nyeri OA dibandingkan dengan Glucosamine Chondroitin**

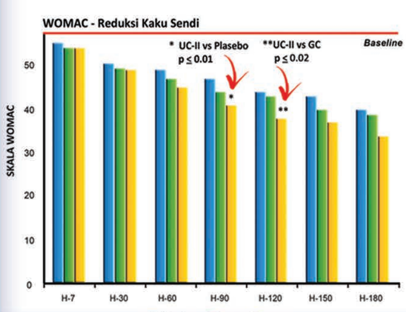



**UC-II lebih efektif mengurangi nyeri OA dibanding Glucosamine Chondroitin**

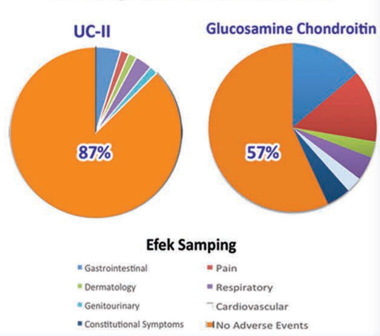
**UC-II lebih efektif mengurangi nyeri OA pada aktivitas sehari-hari**




**UC-II lebih efektif mengurangi kaku sendi OA dibandingkan dengan Glucosamine Chondroitin**




**UC-II 87% dapat ditoleransi lebih baik dibanding Glucosamin & Chondroitin**




# Do we need to perform bilateral hip bone mineral density examination?

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**Abstract**

**Background:** Bone mineral density (BMD) measurement is one of the method for making osteoporosis diagnosis. World Health Organization (WHO) recommends the measurement of BMD conducted at antero-posterior lumbar vertebrae, unilateral hip (femur), and radius. However, there was a concern about osteoporosis under diagnosis if the measurement is only conducted at unilateral hip. Some studies found significant differences of BMD between both femur and evidence of the importance to examine both femur in making the diagnosis of osteoporosis. This study aims to determine anydifference between right and left femur BMD measurement and to investigate the bone status result with measurement of BMD of bilateral femur in Hasan Sadikin General Hospital.

**Methods:** A retrospective study was conducted from June to November 2015. Patients who received dual-femur BMD testing using General Electrics (GE) Lunar Prodigy dual-energy x-ray absorptiometry at the DXA Facility in Hasan Sadikin General Hospital, Bandung between January 1, 2006 to December 31, 2014 were included. Statistical analysis performed to assess the difference and the correlation between the BMD of two femurs (g/cm$^2$). T-scores of the subject were implemented into bone status according to WHO Diagnostic Criteria for Osteoporosis.

**Results:** From sixty-one patients included in this study, there were difference bone status resulted from BMD of the femoral neck, Ward's triangle, trochanter, and total hip area between right and left femur, although no statistically significance were found. There was a positive correlation between BMD of right and left femur at all areas of femur. There were 16 subjects (26.1%) showed combination level of bone status (normal, osteopenia, or osteoporosis in one femur).

**Conclusion:** BMD results in each area of the right and left femurs are different.Therefore, performing bilateral hip BMD examination as a routine measurement for makingdiagnosis of osteoporosis is important.

**Keywords:** Bone Mineral Density, Dual-energy X-ray Absorptiometry, Femur, Osteoporosis

## Background

Osteoporosis is a metabolic disease characterized by low bone mass and deterioration of bone microarchitecture, which can lead to fractures. Based on2013 International Osteoporosis Foundation (IOF) report, the prevalence of osteoporosis in Indonesian is 23% in women aged 50-80 years old, and 53% in women aged 70-80 years old. It is also stated that by 2050 there will be an increase of 135% of osteoporosis prevalence in adult Indonesian over 50 years of age population, and an increase of one-third prevalence of high-risk osteoporosis population.[1] Therefore, it is important to prevent, diagnose, and giving appropiate intervention before the complications occured. The diagnosis of osteoporosis should be made comprehensively, includes: the assessment of history, risk factors, and determination of 10-year fracture probability using FRAX tool; physical examination; bone mineral density (BMD) testing and vertebral imaging. Based on a World Health Organization (WHO) technical report, the National Osteoporosis Foundation (NOF) stated that quantitative measurement of bone mineral content can be achieved by dual-energy X-ray absorptiometry (DXA), at three regions of interest; antero-posterior lumbar vertebrae, femur, and radius. Bone mineral density measurement at the femur is the best predictor of risk for future hip fracture.[2]

In 1994, WHO stated that BMD measurement at unilateral femur was the reasonable and deemed reliable technology available for bone density analysis at the time. Since then, most of BMD measurements are conducted unilaterally, including at Dr. Hasan Sadikin General Hospital Bandung. This action is also supported by the International Society for Bone Densitometry (ISCD), who stated that the measurement can be done at either hip, and the diagnosis is made based on the lowest T-score.[3] However, unilateral measurement does not rule out the diagnosis of osteoporosis on the contralateral hip, especially when spine status is normal.

Some studies have analyzed whether dual-femur examination had clinical importance in establishing the diagnosis of osteoporosis. In 2012, Hwang et al., found 30% rate of T-score discordance between hips, which lead to the underestimation of osteoporosis if only unilateral hip examination was conducted.[4] This is supported by Mounach, et al.(2012) study which determine the prevalence of significant BMD difference between right and left hip and how it influences the classification of bone status. They discovered that the discordance frequency between both hip increases with age, and thus support the need for bilateral femur BMD measurement.[5]

Some clinicians at Hasan Sadikin General Hospital Bandung have ordered dual hip BMD measurement for the diagnosis of osteoporosis. Questions arise about the importance of conducting bilateral hip measurement in diagnosing osteoporosis. Therefore, there may be a possible difference between BMD of both femurs that can affect bone status. However, to the best of our knowledge there has not been any published article regarding the difference of right and left femur BMD in Bandung. This study aims to determine the presence of difference of BMD between both femurs, investigate the resulting bone status produced by bilateral femur BMD measurement, and evaluate whether it is of clinical importance.

## Methods

A retrospective study was conducted in June until November 2015. The population of this study was all patients who received dual-femur BMD testing using General Electrics (GE) Lunar Prodigy dual-energy x-ray absorptiometry at the DXA Facility in Hasan Sadikin General Hospital Bandung. Sample calculation used the equation for numerical analysis with paired data with 95% confidence interval, resulting in 161 subjects for each right and left femur group. Sample were included from data of patients who came between January 1, 2006 and December 31, 2014, and excluded patients whose variables of interest were not recorded. Data collected, include: BMD of both femur which is expressed as grams per centimeter square (g/cm$^2$), patient's age and sex, and osteoporosis risk factors, such as BMI category, elderly status, and menopausal status for women.There were only 61 patients who had undertaken dual-femur testing with all variables recorded, thus included as subject.

The data were analyzed using Microsoft Excel 2010 for Windows and Statistical Package for the Social Sciences (SPSS) version 17. The BMD result of the right and left femur were compared using the Wilcoxon signed rank test ($P<0.05$). The correlation between right and left femur BMD was determined using Spearman's test. Each BMD was compared to the normal young adults of the same age (T-score) and was implemented into bone status according to WHO Diagnostic Criteria for Osteoporosis (Normal >-1.0, Osteopenia -1.0 to -2.5, Osteoporosis ≤-2.5).[2] Chi-square was conducted to establish the association between the bone status of right and left femur. The results were categorized into Normal-normal, Osteopenia-osteopenia, osteoporosis-osteoporosis, and combination (normal-osteopenia, normal-osteoporosis, osteopenia-normal, osteopenia-osteoporosis, osteopenia-osteoporosis and osteoporosis-normal at one hip). The results were presented in the form of tables and figures as appropriate. Ethical clearance for this study was obtained from Health Research Ethical Committee Hasan Sadikin General Hospital (No. LB.04.01/A05/EC/231/VII/2015).

## Results

Sixty-one subjects met the inclusion and exclusion criteria, used as sample in this study. The subject characteristics are presented in Table 1. Subjects was dominated by female (86,9%). Fifty-two of fifty-three female subjects had menopause. Subjects' age varied from 48 to 88 years old, with the median age 67-year-old. There were 34 subjects (55.74%) that were included in the normal BMI category. Forty-one of the subjects (61.27%) were elderly.

**Table 1** Characteristic of Subjects in Dual Femur DXA Measurement

| Characteristic | Result |
|---|---|
| Sex | |
| Female N(%) | 53 (86.9) |
| Male N(%) | 8 (13.1) |
| Age Median (Range) | 67 (48-88) |
| Elderly (above 60 year-old) | |
| Yes N(%) | 41 (61.27) |
| No N(%) | 20 (32.79) |
| BMI Category | |
| Underweight N(%) | 3 (4.92) |
| Normal N(%) | 34 (55.74) |
| Overweight N(%) | 18 (29.50) |
| Obese N(%) | 6 (9.84) |
| Menopause (in female) n=53 | |
| Yes N(%) | 52(98.11) |
| No N(%) | 1(1.89) |

There was a positive correlation between right and left femur BMD at the femoral neck, Ward's triangle, trochanter, and total hip area ($r=0.881$, $p=0.00$; $r=0.791$, $p=0.00$; $r=0.736$, $p=0.00$; and $r=0.815$, $p=0.00$, respectively). The bilateral BMD results were compared. According to the Wilcoxon signed ranks test ($P<0.05$), there was no significant difference between right and left femur BMD at every area. This can be seen in table 2.

**Table 2** Associations of Right and Left Femur BMD at Each Subregion

| Area | Right Femur Median (Range) N=61 | Left Femur Median (Range) N=61 | P value |
|---|---|---|---|
| Trochanter | 0.633 (0.230-1.091) | 0.641 (0.411-1.115) | 0.151 |
| Femoral Neck | 0.798 (0.370-1.319) | 0.756 (0.400-1.354) | 0.926 |
| Ward's Triangle | 0.614 (0.300-0.892) | 0.607 (0.385-1.039) | 0.918 |
| Total Hip | 0.838 (0.377-1.120) | 0.847 (0.448-1.248) | 0.189 |

Bone status of both femurs was obtained from the area with the lowest T-score. The association between the bone status from right and left femur was determined using Chi-square test. Combination of bone status within right and left femur was found in total 16 subjects (26,1%), as followed: 1 subject (1.6%) with normal-osteopenia bone, 1 subject(1.6%) with normal-osteoporosis, 5 subjects(8.2%) with osteopenia-normal, 6subjects (9.8%) with osteopenia-osteoporosis, and 3subjects (4.9%) with osteoporosis-osteopenia. The association between right and left femur bone statuscan be seen in table 3.

**Table 3** Association between Bone Status of Right and Left Femur BMD

| Left Femur Status | Right Femur Status | | | Total |
|---|---|---|---|---|
| | Normal | Osteopenia | Osteoporosis | |
| Normal | 8 (13.1) | 5 (8.2) | 0 (0) | 13 (21.3) |
| Osteopenia | 1 (1.6) | 10 (32.8) | 3 (4.9) | 24 (39.3) |
| Osteoporosis | 1 (1.6) | 6 (9.8) | 17 (27.9) | 24 (39.3) |
| Total | 10 (16.4) | 31 (50.8) | 20 (32.8) | 61 (100) |

**Discussion**

Controversies regarding bilateral femur BMD scanning is still an ongoing issue. The diagnosis of osteoporosis is established based on the lowest T-score at the spine or femur, in a unilateral femur scanning.[2] However, unilateral femur measurement does not rule out the diagnosis of osteoporosis on the contralateral hip, especially when there is a significant difference between the left and right femur BMD.

In this study, there were differences between right and left femur BMD at every area (table 2), although none was statistically significant (P > 0.05). The median BMDs (g/cm$^2$) between right and left femurs were as follows: trochanter 0.633 versus 0.641, femoral neck 0.798 versus 0.756, Ward's triangle 0.614 versus 0.607, and total hip 0.838 versus 0.847. The result was constantly with Hwang, et al. study, who also found the different BMD result of the right and left femur in femoral neck and trochanter area over Korean women with age more than50 years old.[4] However, in their study,the BMD difference in the neck and trochanter area is statistically significance. Within our study, we also found that the Ward's triangle had the smallest median BMD between all areas because of its trabecular structure. As it may produce a false-positive result, the Ward's triangle examination should not be used in making the diagnosis of osteoporosis.[5]

Current study found a strong positive correlation between right and left femur BMD at all areas. The correlation means that the high value of right femur BMD will relate with thehigh value of left femur BMD. This positive correlation might be caused by small absolute differences between the right and left femur, as shown by table 2. Mounach, et al. also found that bilateral femur BMD measurement may be useful in clinical setting. They found strong correlations between right and left BMD at the femoral neck, trochanter, and total hip area.[6] These differences can be caused by genetic variation, immobilization of one limb, and stroke causing hemiplegia.[7,8,9] The difference may also be caused by lack of weight-bearing activity or gait abnormality, associated with a pathologic disease,such as foot or knee pain.[10]

In clinical practice, the bone status for each subject was determined from the area with the lowest T-score. Cross-tabulation was done to see the relationships between right and left bone status. Although the difference of left and right femur BMD was not statistically significant, we found 16 (26.1%) subjects who had combination bone status (table 3). Three of them (4.9%) had osteoporotic bone status in the right femur but osteopenic in the left femur, and 6 subjects (9.8%) had osteopenic bone status in the left femur but osteoporotic in the right femur. This means, if the BMD measurement was only conducted on one-left-femur, there would be 4,9% subjects underdiagnosed as osteopenia, whereas the osteoporotic status ofthe contralateral femur was not found. Thus, the bilateral femur BMD measurement is more benefit than unilateral measurement. In Hwang *et al*. study, bilateral hip measurementalso found useful to prevent underestimation of osteoporosis, as they found 15 (3.9%) of their 384 subjects who had osteopenia but were only diagnosed as normal bone density by unilateral femur BMD measurement.[4]

A study conducted by Hamdy, et al., in 2006 found that there were 16% subjects who had osteoporotic bone status only in the left femur, and 10% subjects whohad osteoporotic bone status only in the right femur.[8] This study is similar to our study in which these patients could benefit from bilateral femur BMD measurement. In this study, the diagnosis was established regardless of the vertebral status to see the difference between right and left femurs. However, there are some studies who determine the vertebral status as normal or osteopenic before establishing the osteoporosis diagnosis at the femurs. The femoral statuses were assumed as osteoporosis if the vertebral status was already osteoporosis.[6, 8]

Some studies compared the T-score values between bilateral and unilateral hip measurements. Cole and Larson found that a bilateral hip BMD measurement led to a change of diagnosis classification to a more severe categories in 9% subjects.[9] In another study, Cole,et al. reported 3.3% population in their study whose diagnosis changed from osteopenia into osteoporosis.[11]It suggests that the difference BMD result between both femurs canbe large enough to change the classification of bone status, if bilateral femurs examination are performed.

Bilateral hip measurement is doable to perform bilateral hip measurement in every suspected osteoporosis cases, as the scanning time became faster with the recent technologies. In Korea, the cost is also no longer an issue.[4,6] However, in Indonesia, the Indonesia National Health Insurance, BPJS, only covers a routine BMD examination, such aslumbar, single hip, and radial area. When a clinician ordered bilateral hip measurement, the patient should pay on themselves. Therefore, the financial issue should be considered before ordering bilateral hip BMD examination.

There were a few limitations of this study. We use aretrospective method study with secondary data as oursubjects. As bilateral femur BMD measurement is not a standard procedure in Dr. Hasan Sadikin General Hospital, there waslimited amount of patients who undertook dual-femur testing. Therefore, the number of samples did not meet the minimum amount of sample and could not be extrapolated to the general population. A prospective cohort would describe the current population better, and further analysis of bilateral BMD testing in all age group should be performed. Besides, our study haven't involve the spine status as predictive value for osteoporosis in each subject. Further analysis about diagnosis value of the spine status for osteoporosis should be performed. This study also have not investigated the influence of individual's side dominance to the BMD level ofthe right and left femur. So, further studies should be conducted to see whether hip dominance plays a role in the right and left BMD measurement, and thus provide a more interesting issue.

**Conclusion**

In conclusion, there were different level of BMDat every area of right and left femurs, but none was statistically significant. There were strong positive correlations of bone status and BMD levelamongall areas in the right and left femur.There were 26.1%population who had combination bone status based on T-score resulted from the BMD of right and left femur BMD. Bilateral femur BMD measurement might be useful in a clinical setting where the patient experiences lack of weight-bearing. The cost issue needs to be considered. Since it is not a routine measurement for osteoporosis diagnosis, before ordering bilateral hip BMD, the clinicians should review how importance is the assesment.

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# Diagnostic values of DAS28 and DAS28-squeeze in evaluating Rheumatoid Arthritis disease

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**Abstract**

**Background :** In recent years, rheumatoid arthritis (RA) uses a "treat to target" treatment strategy. This strategy requires a valid and accurate tool for assessing disease activity. The most widely used tool is DAS28, which was developed from DAS with the omission of ankle and foot joints. There has been many critization about the accuracy of DAS28 in classifying the state of RA disease. Most importantly, when an active disease state was misclassified as an inactive state (false negative) which lead to under treat and subsequently to disability. The difference between DAS28 and DAS lies mainly in the exclusion of ankle and foot joints, thus DAS28-squeeze, a new and simple tool has been proposed. It comprises the same 28 joints in DAS28 added with a sqeeze test on both metatarsophalangeal joints. However, this new tool has never been validated with any imaging techniques.

**Objective :** To assess the diagnostic values of DAS28 and DAS28-squeeze.

**Methods :** This study comprised a cross-sectional diagnostic study, using Power Doppler sonography as a standard reference in evaluating the diagnostic value of DAS28 and DAS28-squeeze. This study uses the most sringent sonography criteria of active disease which is an active Doppler signal with a moderate synovial hypertrophy on B-mode.

**Results :** Over the study period, 56 subjects underwent diagnostic tests using DAS28, DAS28-squeeze and Power Doppler sonography. There were 4 false negative cases in DAS28 and 1 case in DAS28-squeeze. The sensitivities of DAS28 and DAS28-squeeze to identify active disease using Power Doppler sonography as reference standard were 73.3% (95%CI ± 11.59) and 93.3% (95%CI ± 6.55), respectively. While the specificities of DAS28 and DAS28-squeeze were 36.6% (95%CI ± 12.62) and 34.1% (95%CI ± 12.42), respectively. Furthermore the negative likelihood ratio of DAS28 and DAS28-squeeze were 0.73 and 0.19, respectively.

**Conclusion :** This study is the first to validate DAS28-squeeze using imaging techniques. From this study the false negative rate of DAS28-squeeze is lower than DAS28. DAS28-squeeze has a better sensitivity and negative likelihood ratio than DAS28 in identifying RA disease state.

**Keywords :** Rheumatoid Arthritis, DAS28, DAS28-squeeze, treat to target, Power Doppler, squeeze test

## Introduction

In the past two decades, there has been significant advancement in the understanding of Rheumatoid Arthritis (RA) pathophysiology and therapeutic modalities. Therefore, the need of early detection, early therapy initiation, and tight control of disease activity have risen. Recently, rheumatologists adopted the "treat to target" therapeutical protocol for treating early RA. [1-4] The main strategy of the therapy is assessing disease activity on a regular basis to achieve a certain target. In daily practice disease activity assessment is usually done with Disease Activity Score 28 (DAS28) because it is clinically applicable.[1-3] DAS28 has been developed and validated using data from clinical research. Unfortunately, a valid instrument developed from a set of clinical research data is not neccesary became a valid instrument in daily practice.[5] Thus, a new instrument called DAS28-squeeze developed to assess RA disease activity in clinical practice. This new instrument has never been validated by imaging techniques. Thus, we attempt to assess the diagnostic values of DAS28 and DAS28-squeeze using power doppler sonography as a standard reference.

DAS28 was originally developed from Disease Activity Score (DAS) which was published by van der Heijde, et al. in 1990. The original DAS comprises of 4 components, a 44 swollen joint count, Ritchie articular index (RAI), erythrocyte sedimentation rate (ESR) and patient global assesment of disease.[6] Because this instrument isn't practically used in clinical settings, in 1994, Prevoo, et al. proposed a modified DAS which comprises only 28 swollen and tender joint count, and excludes the feet and RAI. The modified DAS is now known as DAS28.[7] DAS28 formula is presented below.[1]

$$\mathbf{DAS28 = 0.56 \times \sqrt{(28TJC)} + 0.28 \times \sqrt{(28SJC)} + 0.70 \times Ln(ESR/CRP) + 0.014 \times VAS}$$

Abbreviation list:

- TJC = *Tender Joint Count* (jumlah sendi yang nyeri)
- SJC = *Swollen Joint Count* (jumlah sendi yang bengkak)
- ESR = *Erythrocyte Sedimentation Rate* (Laju Endap Darah [LED])
- CRP = *C-reactive protein*
- VAS = *Visual Analogue Scale*

DAS28 calculation then can be classified as follows:

- Remission : DAS28 ≤ 2.6
- Low disease activity : 2.6 < DAS28 ≤ 3.2
- Moderate disease activity : 3.2 < DAS28 ≤ 5.1
- High disease activity : DAS28 > 5.1

DAS28 comprises 28-joint, by excluding joints of the feet and ankle. The shortage of DAS28 lies when assessing patient who suffers of inflamation only in his/her feet and ankle joint. DAS28 will classified such a patient as in remission state (inactive disease activity). This could lead to a false negative misclassification, where an active disease activity classified as in a remission state.[1,5,6] Literatures stated that up to 40% patients classified as remission by DAS28 still have feet complaints (swollen and/or tender on at least one metatarsophalangeal [MTP] joint).[1,8,10,11] Further, remission patients, according to DAS28, were also found to have a significant swollen joint counts. [1,8,10,11]

Feet complaints as an initial symptoms has been found in 60% of RA patients, and after 2 years the feet involvement prevalence decreases to 36%. This feet involvement is an important factor to cause disability in subsequent RA disease proggression. [1, 7-9]

Assessing MTP joints inflamation (synovitis) in daily clinical settings is cumbersome. Thus, a simple test has been proposed to assess synovitis in feet joints to improve disease activity measurement, which in turn will influence the subsequent therapeutic decision making. This test is the MTP joints bilateral squeeze test which assess the bilateral compression pain (BCP). [1, 10]

DAS28 which modified by adding MTP squeeze test is called DAS28-squeeze. It is developed using linear regression model using DAS as a dependent variable and DAS28 and MRP squeeze test as an independent variables. The squeeze test results are categorized as follows: 0 for negative test (no pain on both feet), 1 for pain on one foot, 2 for pain on both feet. De Jong, et al. defined the disease activity state for DAS28-squeeze as follows: below 1.6 for remission, 1.6 - 2.4 for moderate disease activity and above 2.4 for high disease activity. Whereas the DAS28-squeeze formula is 0.64 x DAS28 + 0.23 x squeeze test result. This new instrument has also never been validated by imaging techniques. de Jong, et al. stated that imaging validation is required to assess DAS28-squeeze validity.[1]

Up till now, RA disease activity assessment in clinical settings has relied on DAS28. Disease activity assessment is an important aspect of RA management because theraupetical decision is given based on the disease activity state. If DAS28 is inaccurate to classify RA disease activity, patients would get suboptimal therapy which leads to rapid disease progression and ultimately to disability. In this study, we would like to assess the diagnostic values of DAS28 and DAS28-squeeze comparing with power doppler sonography as a reference standard.

**Methods**

This study is a diagnostic study using power doppler sonography as reference standar. Study subjects are patients visiting Cipto Mangunkusumo hospital Rheumatology outpatient clinic between August to December 2015 period who fulfilled the 2010 ACR/EULAR criteria for rheumatoid arthritis and who were willing to be tested using power doppler sonography and didn't suffer from any infection (tuberculosis, pneumonia, urinary tract infection, other bacterial infection) that might influence their ESR result. Calculated sample size were 47 patients, this was achieved using the following formula.

$$n = \frac{(Z\alpha)^2\ Sen(1-Sen)}{d^2P}$$

Sensitivity was set at 90%, study precision (d) was set at 10%, Zα was set at 1.96 and prevalence (P) of active disease was set at 75%.

Sampling was done using consecutive sampling method. Diagnostic values of DAS28 and DAS28-squeeze were stated as sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio using 95% conficence interval. All calculations were done using Statistical Packages for Social Sciences (SPSS) version 20.

Squeeze test was done by one single examiner on both metatarsophalangeal (MTP) joints by placing thumb and index finger, respectively, just below the first MTP joint and over the fifth MTP joint. The thumb is placed just below the first MTP joint to prevent direct compression of the joint. Then, the metatarsal joints are bilaterally compressed, using a force equal to handshake. The squeeze test was coded as follows: 0 = test negative on both forefeet, 1 = test positive on 1 side, 2 = test positive on both forefeet.[1]

Power doppler ultrasonography (PDUS) was done by one single radiologist experienced in musculoskeletal ultrasonography. The radiologist was blind about the result of DAS28 and MTP squeeze of each subject. PDUS were used to examine joints as stated in US7 joints, include wrist, second and third metacarpophalangeal and proximal interphalangeal, and second and fifth metatarsophalangeal joints.[11] Grey-scale imaging evaluation confirmed the presence or absence of synovial hypertrophy (SH) and/or joint effusion, which was graded using a semiquantitative scoring method consisting of a scale of 0–3, where 0 represented no SH, 1 mild hypertrophy, 2 moderate hypertrophy and 3 severe hypertrophy. PD was stated as 0 represented no signal and 1 as positive power doppler signal. [12] Synovitis on PDUS was defined using the most stringent PDUS criteria which is SH ≥ 2 with positive doppler signal. [12, 13]

**Results**

Fifty six subject (49 females and 7 males) were included in this study. Study subject characteristic can be seen in Table 1.

**Table 1.** Study subject characteristic

| Subject characteristic | N | % |
|---|---|---|
| 1. Sex | | |
| Male | 7 | 12.5 |
| Female | 49 | 87.5 |
| 2. Age Group | | |
| 21-30 years old | 3 | 0.05 |
| 31-40 years old | 10 | 17.86 |
| 41-50 years old | 11 | 19.65 |
| 51-60 years old | 17 | 30.36 |
| > 60 years old | 15 | 26.78 |
| 3. Disease duration | | |
| ≤ 2 years | 20 | 35.72 |
| > 2 years | 36 | 64.28 |
| 4. Feet complaints | | |
| Present | 25 | 44.64 |
| None | 31 | 55.36 |
| 6. Medication | | |
| MTX | 32 | 57.14 |
| SFZ | 3 | 0.05 |
| MTX + SFZ | 5 | 0.09 |
| MTX + MP | 13 | 23.21 |
| SFZ + MP | 2 | 0.03 |
| MTX + SFX + MP | 1 | 0.01 |
| 5. Body Mass Index | | |
| Underweight | 3 | 0.05 |
| Normal | 22 | 39.28 |
| Overweight | 31 | 55.35 |

MTX = Methotrexate, SFZ = Sulfasalazine, MP = Metilprednisolon

Study subject were predominantly women (87.5%), most were between 51-60 years old (30.36%), with mean age of 50.6 years old. Most of the patients (64.28%) who visited Cipto Mangunkusumo hospital Rheumatology outpatient clinic suffers from chronic RA, with mean disease duration of 4.8 years. Twenty five (44.64%) patients had feet complaints.

**DAS28 and DAS28-squeeze**

Below are presented the result of DAS28 and DAS28-squeeze test.

**Table 2.** DAS28 and DAS28-squeeze results

| Instrument | n | % |
|---|---|---|
| DAS28 | | |
| Inactive | 19 | 33.93 |
| Active | 37 | 66.07 |
| DAS28-squeeze | | |
| Inactive | 15 | 26.78 |
| Active | 41 | 73.22 |

DAS = Disease Activity Score

**Kappa score for sonography test**

To assess the reliability of sonography examination, we decided to repeat the sonography examination on 10% of the total estimated sample, resulted in five subjects on all seven joints included in the examination with totally 35 joints. The first and second sonography examination was done on the same day to avoid any changes on the synovitis activity. All sonography examinations were done by the same examiner. From the examinations a 2x2 table could be constructed as follows.

**Table 3** Sonography Kappa test

| positive | | ***First Test*** | | total |
|---|---|---|---|---|
| | | negative | | |
| ***Second Test*** | Positive | 17 | 3 | 20 |
| | Negative | 4 | 11 | 15 |
| | Total | 21 | 14 | 35 |

The Kappa score result according to SPSS version 20 was 0.588 which reflected a moderate to good reliability.

**Diagnostic Test Results**

From the study data we could construct 2x2 tables of DAS28 and DAS 28-squeeze, as follow.

**Table 4.** DAS28 diagnostic test

| Active | | **USG** | | n |
|---|---|---|---|---|
| | | Inactive | | |
| **DAS28** | Active | 11 | 26 | 37 |
| | Inactive | 4 | 15 | 19 |
| | Total | 15 | 41 | 56 |

**Table 5.** DAS28-squeeze diagnostic test

| Active | | **USG** | | n |
|---|---|---|---|---|
| | | Inactive | | |
| **DAS28-squeeze** | Active | 14 | 27 | 41 |
| | Inactive | 1 | 14 | 15 |
| | Total | 15 | 41 | 56 |

Based on the tables we could calculate DAS28 diagnostic values as follows; sensitivity 73.3%% (95%CI ± 11.59), specificity 36.6% (95%CI ± 12.62), positive predictive value 29.7% (95%CI ± 11.97), negative predictive value 78.9% (95%CI ± 10.69), positive likelihood ratio 1.15 and negative likelihood ratio 0.73. And DAS28-squeeze diagnostic values; sensitivity 93.3% (95%CI ± 6.55), specificity 34.1% (95%CI ± 12.42), positive predictive value 34.1% (95%CI ± 12.42), negative predictive value 93.3% (95%CI ± 6.55), positive likelihood ratio 1.41 and negative likelihood ratio 0.19.

**Discussion**

Synovial hypertrophy on B-mode sonography was found in 91.07% of wrist joints examinations, this finding is consistent with Doron et al study which concluded around 75% of early RA patients have wrist complaints and could increase to up to 95% in chronic RA[14] Vlad, et al. study concluded that power doppler sonography is the best modality in assessing pathological activity in wrist and finger joints. They also concluded that wrist joint is the most prevalently affected joint in RA.[14]

The low specificity result in this study could attribute to the high false positive number in both DAS28 and DAS28-

squeeze. Which means many patients that were in an active disease state according to DAS28 and DAS28-squeeze were found to be inactive according to sonography examination. There are a few possible explanations for this high number of false positive. First, many patients that have swollen and tender joints were found to be inactive according to sonography. This is possible because most patients included in this study are suffered from chronic RA which resulted in synovial thickening, thus making it more difficult to detect blood flow on power doppler sonography. Other explanation is that many patients have already developed joint deformity which resulted in pain on joint counts, but not neccesarily reflects the active inflammation state.[15] Second, the formula used in DAS28 emphasizes too much on ESR, thus little increase in ESR produced a significant increase in DAS28 result.[5] Since DAS28-squeeze uses DAS28 result in its calculation, the value would also be significantly increased. The third possibility is undetected synovitis by sonography examination. This is caused by several reason, such as: (1) excessive pressure applied on examination area; (2) low skin temperature resulted in decrease in Doppler activity, thus cleaning with water prior to examination should be avoided; (3) lack of gel applied; (4) diurnal variation in Doppler activity; (5) sonography equipment settings. [13, 16, 17] However a negative Doppler signal doesn't always reflected an inactive disease state. [13]

In this study all avaoidable factors that could resulted in undetection of Doppler activity have been anticipated. Gel application was adequate, excessive pressure wasn't applied, water wasn't applied prior to examination, equipment settings were good and the operator was experienced in musculoskeletal sonography. This study uses the most stringent sonography criteria in defining active synovitis.

False positive in DAS28 and DAS28-squeeze were found in 28 and 26 cases, respectively. The consequences of the false positivity is an over treatment in treating RA patients. DAS28-squeeze sensitivity of 93.3% (95%CI ± 6.55) shows that this instrument is quiet good for screening purpose. A likelihood ratio of 0.19 also indicating that it is good enough to rule out the disease, because ideally it should be below 0.1. DAS28-squeeze power in ruling out active disease state is far better than DAS28, which can be seen from DAS28 sensitivity and negative likelihood ratio of just 73.3% (95% CI ± 11.59) and 0.73 respectively. From the likelihood ratio results we can calculate the post-test probability of each instrument as follows:

**Table 6** Post-test probability results

| Pretest Prob-ability | Pre-test Odds | Positive Post-test Odds | | Negative Post-test Odds | | Positive Post-test Probability | | Negative Post-test Probability | |
|---|---|---|---|---|---|---|---|---|---|
| | | DAS 28 | DAS 28-squeeze | DAS 28 | DAS 28-squeeze | DAS 28 | DAS 28-squeeze | DAS 28 | DAS 28-squeeze |
| 75% | 3 | 3.45 | 4.23 | 2.19 | 0.57 | 77.5% | 80.9% | 68.6% | 36.3% |

False negative were found in 4 cases and 1 case in DAS28 and DAS28-squeeze respectively. False negativity in RA management should be avoided because it could lead to under treatment which could ultimately resulted in disability. This study results are in line with the initial goal of DAS28-squeeze in avoiding false negative misclassification.

## Conclusion

This study is the first study which evaluates diagnostic values of DAS28-squeeze using imaging techniques as reference, particularly using power doppler sonography criteria in detecting active RA disease activity state. The limitation of this study primarily lies in the characteristic of subject where most of them suffer from chronic RA which resulted in harder Doppler activity detection. In conclusion DAS28-squeeze has better diagnostic values than DAS28 in evaluating RA disease activity state using power doppler sonography as reference.

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# Predictor Factors of Atherosclerosis and Atherosclerosis Plaque in Rheumatoid Arthritis Patients

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**Abstract**

**Background:** Atherosclerosis and cardiovascular diseases have been known as the cause of increasing mortality among rheumatoid arthritis (RA) patients. Carotid intima media thickness (CIMT) measurement by ultrasound has been used as surrogate marker of atherosclerosis and cardiovascular disease.

**Methods:** A cross sectional study of 86 RA patients fulfills EULAR/ACR 2010 critera for RA was conducted to study proportion and predictor factors of atherosclerosis and atherosclerosis plaque in rheumatoid arthritis patients.

**Results:** Atherosclerosis and plaque was found in 47,7% and 29 % of patients. Age ≥ 40 yo, hypertension and duration of illness ≥ 24 mo were associated with atherosclerosis in multivariate logistic regression analysis with OR 10.70 (95% CI: 2.93-39.10), 4.99 (95% CI: 1.15-21.61) and 3.66 (95% CI: 1.11-11.99) respectively. Whereas hypertension, presence of anti-CCP antibody and age ≥ 40 yo, were associated with plaque formation with OR 3.96 (95% CI: 1.15-13.57), 3.20 (95% CI: 1.11-9.24) and 3.61 (95% CI: 1.03-12.63) respectively.

**Conclusions:** Age ≥ 40 yo, hypertension and duration of illness ≥ 24 mo was the predictors of atherosclerosis, while hypertension, presence of anti-CCP antibody and age ≥ 40 yo was the predictors of atherosclerosis plaque.

**Key words:** atherosclerosis, intima media thickness, predictor, rheumatoid arthritis, ultrasonography.

## Introduction

Rheumatoid Arthritis (RA) is a rheumatoid disease marked by the presence of autoimmunity and systemic chronic inflammation. This chronic disease, which occurs in 0.5 – 1.0% of population, causes progressive polyarthritis inflammation and joints damage.[1] Other than the increase in morbidity associated with the joint damage, RA patients are also associated with increased mortality when compared to the normal population.[2,3] The mechanism by which increase cardiovascular mortality occurs in RA patients is a complex one. The increase in cardiovascular morbidity and mortality in RA patients may not be completely attributed to the traditional risk factors such as obesity, dyslipidemia, diabetes mellitus, hypertension, and smoking.[4,5] This chronic inflammatory condition in RA causes not only synovitis of the joints, but also causes, and is related to, the development of atherosclerosis and/or atherosclerotic plaques in the vascular system.

The atherosclerosis and cardiovascular diseases are appears to be the primary cause of early death in RA and other autoimmune diseases, as compared to the normal population. Myocardial infarction, ischemic heart disease, heart failure, sudden death, and stroke have become the primary causes for the increasing cardiovascular mortality.[4-6]

As a result, comprehensive assessment and treatment of the traditional and non-traditional cardiovascular risk factors is an important part of the routine management of RA patients.[6] The proper identification and stratification of RA patients with a high risk and the immediate treatment is an important part in the management of rheumatoid diseases such as RA.

## Methods

This is a cross-sectional research which was performed at Dr. Cipto Mangunkusumo National General Hospital (RSCM) in Jakarta from October 2012 – March 2013. The subject of this research was patients with RA who came for treatment at the Rheumatology clinic at RSCM, Jakarta; fulfilled the inclusion criteria; and did not fulfill the exclusion criteria. The inclusion criteria employed in this study were RA patients with aged minimum 16 years old when the diagnosis was made, fulfilled the RA criteria of EULAR/ACR 2010, and were willing to participate in this study and have signed the informed consent form. The exclusion criteria were subjects who were pregnant or lactating; those who suffered from a malignant disease; has a history of consuming biologic agents; has a history of myocardial infarction, stroke, or peripheral arterial disease.

The collected data included: the length of time since RA diagnosis, patient age, the presence of risk factors such as hypertension, smoking, type 2 diabetes mellitus, obesity, dyslipidemia, serum anti-CCP antibody levels, antioxidized - LDL antibody levels, hand and foot radiology examination to assess RA severity (Sharp ve Heijde Score), Carotid USG examination to assess CIMT and atherosclerotic plaque. The analyzed variables were categorized into groups of yes and no, and associated with the presence of atherosclerosis and atherosclerotic plaques.

Hypertension was defined using the JNC VII;[7] DM II based on The Indonesian Society of Endocrinology (PERKENI) 2011 criteria for diagnosis;[8] smoking was based on the CDC definition;[9] dyslipidemia based on NCEP/ATP III;[10] obesity was defined as BMI ≥ 25kg/m$^2$;[11]serum anti-CCP antibody levels and antioxidized-LDL antibody levels were considered positive if the results were > 25 U/mL dan > 30 U/mL, respectively.

USG examination was performed by a professional and full trained radiologist to determine the presence of atherosclerosis and atherosclerotic plaques using the standardized method with B-mode Philips® Sonos 5500 USG and a high frequency linear transducer (>7 MHz). Atherosclerosis was defined by CIMT ≥ 1,0 mmat the common carotid artery, and/or the internal carotid artery, and/or carotid bulb on the left and/or right side.[12-15] Atherosclerotic plaque was determined by the presence of one of the following during the atherosclerosis examination: abnormal CIMT(≥1,5mm), abnormal shape (bulging into the lumen, loss of alignment with the arterial wall), presence of abnormal wall texture (echo brighter that the surrounding border).[12-15]

### Results

In this research, we included 120 RA patients. From the 120 subjects, we have 93 subjects. Three patients were dropped out due to refuse undergone blood test, USG, and other radiological examination. Further, 4 others patients also refused to undergo the USG and radiology examination after undergoing the blood test. Finally, 86 subjects participated in this study, with complete medical history, laboratory examination, carotid USG and radiology. From the 86 subjects who were analyzed, atherosclerosis was found in 41 subjects (47.7%) and atherosclerotic plaque in 25 subjects (29%). The subjects comprised of eight males (9.3%) and 78 females (90.7%). Other subject characteristics can be seen in Table 1. The carotid artery thickness can be seen in Table 2.

**Table 1.** Subject Demographics

| Variable | Total No. of Subjects N = 86 | Atherosclerosis No N = 45 | Atherosclerosis Yes N = 41 | Atherosclerotic Plaque No N =61 | Atherosclerotic Plaque Yes N = 25 |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male (%) | 8 (9,3) | 4 (4,65) | 4 (4,65) | 4 (4,6) | 4 (4,6) |
| Female (%) | 78 (90,7) | 41 (47,67) | 37 (43,0) | 57 (66,3) | 21 (24,4) |
| Age (years)* | 49,5 (20-70) | 38 (20-61) | 56 (28-70) | 43(20-70) | 56 (28-69) |
| Duration of disease (months)* | 25,5 (2-233) | 17 (2-133) | 36 (3-233) | 23 (2-145) | 28 (3-233) |
| Treatment (%) | | | | | |
| Methyl prednisolon | 63 (73,3) | | | | |
| MTX | 54 (62,8) | | | | |
| SSZ | 17 (19,8) | | | | |
| MTX+SSZ | 15 (17,4) | | | | |
| Dosage* | | | | | |
| Methyl pred(mg/day) | 4 (0-16) | 4 (0-16) | 4 (0-16) | 4 (2-16) | 4 (2-16) |
| MTX (mg/week) | 11,25 (SD 3,4) | 10 (7,5-17,5) | 10 (7,5-20) | 10 (7,5-20) | 12,5 (7,5-20) |
| SSZ (g/day) | 1 (1-2) | 1 (1-2) | 1 (1-2) | 1,28 (SD 0,45) | 1,11 (SD 0,33) |
| DAS 28 Score* | 3,7 (2,09-6,47) | 3,62(2,09-6,03) | 3,70(2,58-6,47) | 3,7 (2,09-6,03) | 3,5 (2,70-6,47) |
| Remission (<2,6) | 5 (5,8) | | | | |
| Mild (≤3,2) | 17 (19,8) | | | | |
| Moderate (>3,2≤5,1) | 56 (65,1) | | | | |
| Severe (>5,1) | 8 (9,3) | | | | |
| BMI (kg/m$^2$) | 23,9 (SD 4,41) | 23,68 (SD 4,66) | 24,05 (SD 4,18) | 23,7 (SD 4,53) | 24,30(SD 4,17) |
| ESR(mm/1hour)* | 45 (5-135) | 48 (5-135) | 40 (10-110) | 49 (10-135) | 33 (5-99) |
| CRP (%) | | | | | |
| Negative | 41 (47,7) | 20 (44,4) | 21 (51,2) | 28 (45,9) | 13 (52,0) |
| Positive | 45 (52,3) | 25 (55,6) | 20 (48,8) | 33 (54,1) | 12 (48,0) |
| Rheumatoid Factor (%) | | | | | |
| Negative | 31 (36,0) | 18 (0,4) | 13 (31,7) | 22 (36,1) | 9 (36,0) |
| Positive | 55 (64,0) | 27 (0,6) | 28 (68,3) | 39 (63,9) | 16 (64,0) |
| Anti-CCP Antibody (%) | | | | | |
| Negative | 53 (61,6) | 28 (62,2) | 25 (61,0) | 41 (67,2) | 12 (48,0) |
| Positive | 33 (38,4) | 17 (37,8) | 16 (39,0) | 20 (32,8) | 13 (52,0) |
| Anti ox-LDL (%) | | | | | |
| Negative | 22 (25,6) | 10 (22,2) | 12 (29,3) | 14 (23,7) | 8 (32,0) |
| Positive | 62 (72,1) | 33 (71,1) | 29 (70,7) | 45 (76,3) | 17 (68,0) |
| Hypertension (%) | | | | | |
| No | 70 (81,4) | 41 (91,1) | 29 (33,72) | 53 (86,9) | 17 (68,0) |
| Yes | 16 (18,6) | 4 (8,9) | 12 (13,95) | 8 (13,1) | 8 (32,0) |
| Type 2DM (%) | | | | | |
| No | 82 (95,35) | 45 (100) | 37 (90,2) | 60 (98,4) | 22 (88,0) |
| Yes | 4 (4,65) | 0 (0,0) | 4 (9,8) | 1 (1,6) | 3 (12,0) |
| Dyslipidemia (%) | | | | | |
| No | 58 (67,4) | 32 (71,1) | 26 (63,4) | 42 (68,9) | 16 (64,0) |

| | | | | | |
|---|---|---|---|---|---|
| Yes | 28 (32,6) | 13 (28,9) | 15 (36,6) | 19 (31,1) | 9 (36,0) |
| Smoking (%) | | | | | |
| No | 85 (98,8) | 45 (100) | 40 (97,6) | 61 (100) | 24 (96,0) |
| Yes | 1 (1,2) | 0 (0,0) | 1 (2,4) | 0 (0,0) | 1 (4,0) |
| Obesity (%) | | | | | |
| No | 49 (57,0) | 27 (0,6) | 22 (53,7) | 37 (60,7) | 12 (48,0) |
| Yes | 37 (43,0) | 18 (0,4) | 19 (46,3) | 24 (39,3) | 13 (52,0) |
| Sharp van Heijde Score* | | | | | |
| Total | 32 (0-355) | 28(0-355) | 40(2-121) | 31 (0-355) | 40 (2-107) |
| Hand | 20 (0-271) | 17 (0-271) | 23 (1-97) | 19 (0-271) | 23 (1-95) |
| Foot | 10 (0-84) | 9 (0 - 84) | 11 (0 - 24) | 9 (0- 84) | 11 (0-21) |

* Median (minimum-maximum), SD: Standard Devia tion

**Table 2.** Carotid Artery CIMT

| Artery | CIMT (min-max) mm |
|---|---|
| Common Carotid Artery | 0,683 (0,39-1,94) |
| Internal Carotid Artery | 0,705 (0,45-2,04) |
| Carotid Bulb | 0,850 (0,38-4,34) |

Bivariate analysis showed that the predicting factors associated with the presence of atherosclerosis in RA were patients aged ≥ 40 years, duration of illness ≥ 24 months, hypertension and type 2DM. The predicting factors associated with the presence of atherosclerotic plaque in RA patients were age ≥ 40 years; duration of illness ≥ 24 months; hypertension;type 2DM; and the anti CCP antibody status. Smoking was not included in the bivariate analysis or the multivariate analysis because only 1 subject was a smoker.

Variables in the bivariate analysis with p value < 0.25 were age ≥ 40 years, illness duration ≥ 24 months, hypertension,and type 2DM were included in the multivariate analysis for atherosclerosis. The variables age ≥ 40 years, illness duration ≥ 24 months, hypertension, type 2DM, and the anti CCP antibody status were included in the multivariate analysis for atherosclerotic plaques. The multivariate analysis of the variables can be seen in Table 3 and 4.

**Table 3.** Atherosclerosis Multivariate Analysis

| Variable | OR (95%CI) | p |
|---|---|---|
| Age > 40 years | 10,70 (2,93-39,10) | <0,001 |
| Hypertension | 4,99 (1,15-21,61) | 0,031 |
| Duration of illness ≥ 24 months | 3,66 (1,11-11,99) | 0,032 |

**Table 4.** Atherosclerotic Plaque Multivariate Analysis

| Variable | OR (95%cl) | p |
|---|---|---|
| Hypertension | 3,96 (1,15-13,57) | 0,029 |
| Anti CCP Antibody | 3,20 (1,11-9,24) | 0,031 |
| Age ≥ 40 years | 3,61 (1,03-12,63) | 0,044 |

Multivariate analysis revealed that the variables with statistical significance for the occurrence of atherosclerosis, in order, were age ≥ 40 years, hypertension, and illness duration ≥ 24 months; whereas for atherosclerotic plaque, in order, were hypertension, Anti CCP antibody status, and age ≥ 40 years.

To predict the probability of atherosclerosis and atherosclerotic plaque, multivariate analysis provided the regression coefficient for each variable. Based on the analysis, the probability for atherosclerosis and atherosclerotic plaques were each calculated using the specific model equation based on the presence of specific variables in the individual.

The probability model equation obtained was:

For atherosclerosis, the equation for probability was = P = 1/ 1+ $e^{-y}$

e = constant, 2.7

y = the equation obtained from multivariate analysis using logistic regression, for atherosclerosis y = -(-3,068 + 2,370 [age ≥ 40 years] + 1,296 [duration of illness ≥24 months] + 1,608 [hypertension]),

Therefore P =

$$\frac{1}{1+ e^{-(-3,068 + 2,370 \text{ [age} \geq 40 \text{ years]} + 1,296 \text{ [duration of illness} \geq 24 \text{ months]} + 1,608 \text{ [hypertension])}}}$$

For atherosclerotic plaque, the probability =

$$\frac{1}{1+ e^{-(-2,634 + 1,285 \text{ [age} \geq 40 \text{ years]} + 1,376 \text{ [hypertension]} + 1,164 \text{ [anti-CCP status])}}}$$

To simplify and allow easy use of the probability prediction for atherosclerosis and atherosclerotic plaque in daily practice, thus a scoring system was constructed. The use of this scoring system allows easier identification and stratification of RA patients with a high cardiovascular risk.

The prediction score for atherosclerosis and atherosclerotic plaque for each variable was made based on the rounding of the result from the division of the regression coefficient with the standard error (SE) from each predicting variable. Thus, the score for each variable (Table 5 and 6), are obtained.

**Table 5.** Atherosclerosis Prediction Score

| Variable | B | SE | B/SE | Score | Rounded To |
|---|---|---|---|---|---|
| Age ≥ 40 years | 2,370 | 0,661 | 3,585 | 1,67 | 2 |
| Duration of illness ≥24 months | 1,296 | 0,606 | 2,139 | 1,00 | 1 |
| Hypertension | 1,608 | 0,747 | 2,152 | 1,01 | 1 |

**Table 6.** Atherosclerotic Plaque Prediction Score

| Variable | B | SE | B/SE | Score | Rounded To |
|---|---|---|---|---|---|
| Age ≥ 40 years | 1,285 | 0,638 | 2,014 | 1,00 | 1 |
| Anti-CCP Status | 1,164 | 0,541 | 2,152 | 1,07 | 1 |
| Hypertension | 1,376 | 0,629 | 2,186 | 1,09 | 1 |

Based on the available score for each variable, with the logistic regression, a total score can be obtained, thus allowing measurement of the probability for atherosclerosis and atherosclerotic plaque based on the total score for every individual.

For atherosclerosis, the probability, based on the total score, can be calculation using the following equation:

$$\frac{1}{1+e^{-(-3{,}077\ +\ 1{,}248\ [\text{total score}])}}$$

From this equation, the probability for each total score can be calculated (Table 7).

**Table 7.** The Probability of Atherosclerosis Based on the Total Score

| Total Score | Probability of Atherosclerosis |
|---|---|
| 0 | 4,5 % |
| 1 | 14 % |
| 2 | 36 % |
| 3 | 66 % |
| 4 | 76% |

For atherosclerotic plaque, the probability can be calculated based on the total score by the following equation:

$$\frac{1}{1+e^{-(-2{,}638\ +\ 1{,}265[\text{total score}])}}$$

From this equation the probability for each score can be calculated (Table 8).

**Table 8.** Probability of Atherosclerotic Plaque Based on the Total Score

| Total Score | Probability of Atherosclerotic Plaque |
|---|---|
| 0 | 7 % |
| 1 | 20 % |
| 2 | 47 % |
| 3 | 76 % |

The prediction score for atherosclerosis and atherosclerotic plaque have been tested for the quality or performance by calibration test (Hosmer-Lemeshow Test) and for discrimination ability by observing the result of the under receiver operating characteristic curve[AUC].In the atherosclerotic prediction score the Hosmer Lemeshow got a result of p = 0.794(p > 0.05) which indicates that the precision is good. Similarly, the discrimination ability to differentiate patients who will suffer atherosclerosis from those who will not have atherosclerosis was also good (AUC = 0.800; 95% CI 0.707 - 0.892).For the prediction of atherosclerotic plaque occurrence, the Hosmer Lemeshow score p = 0.696(p > 0.05) which indicates that the prediction model has good precision. The discrimination ability of the atherosclerotic plaque prediction score based on the AUC is moderate (AUC = 0.719; 95% CI 0.599-0.839).

The second internal validation of the scoring system was done using the Bootstrapping method. Following validation, the Hosmer Lemeshow test gave a p value of 0.838 and 0.956 for atherosclerosis and atherosclerotic plaque, respectively. The Hosmer-Lameshow p value > 0.05 after the Bootstrapping method was done to show that the two prediction scores were internally validated ina proper manner.

**Discussion**

This research involved 86 subjects, eight (9.3%) males and 78 females (90.7%). However, this observation varies from previous research which show that the proportion of males to females is 3 : 4. This may be caused by the difference in the population, location of research, and inclusion and exclusion criteria. Further, the median age of subjects in this research is 49.5 years. The youngest subject being 20 years old and the oldest 70 yeasr old. Similar results are reported in other studies which show that RA is most commonly found in the $4^{th}$ – $5^{th}$ decades. Furthermore, the duration of illness in the subjects of this study ranged from 2 months till 9.7 years.

Disease activity, as assessed by the DAS-28LED Score, was moderate in majority of the patients (65%). High disease activity was found in 9% of the subjects, low activity in 20% of the subjects, and only 6% were in remission. The small proportion of patients in remission and a low average weekly MTX dose (11.25 mg), and the limited types of DMARDs available appear to be correlated. This may be attributed to the limited DMARD options available at the medical formularium and the lack of funds among the patients. Moreover, this small percentage of patients in remission necessitates additional consideration and further research.

Atherosclerosis (CIMT ≥ 1.0mm) and atherosclerotic plaque were found in 41 subjects (47.7%) and 25 subjects (29%), respectively. The cut-off for CIMT of ≥ 1.0mm was used in this study is considered to increase the risk for a cardiovascular event in the future. This cut-off is also the level used by the Radiology Department at FKUI/RSCM Jakarta where USG examination and other research are conducted.[12,14,15]

The proportion of subjects with atherosclerosis and atherosclerotic plaques were different compared to previous studies. This may be attributed to the difference in definition, cut-off values, population, examination methods, location, and measuring instruments used. Different academic centers and research groups have different cut-off values, methods and examination approaches.[16]

Gender was not identified as a significant risk factors with the occurrence of atherosclerosis by bivariate and multivariate analysis. In this study, there were only eight male subjects (9.3%) with a proportion of 1 : 10 compared to the number of female subjects, lower than the proportions mentioned in the literature. Currently, no research has ever reported the association of a specific gender with the occurrence of atherosclerosis in RA patients.

In this research, age ≥ 40 years and duration of illness ≥ 24 months are significantly associated with the occurrence of atherosclerosis. Through logistic regression analysis on atherosclerosis, the OR for age ≥ 40 years and duration of illness ≥ 24 months were 10.7 (CI 95% 2.93 – 39.1; p < 0.001) and 3.66 (CI 95% 1.11 – 11.99; p = 0.032), respectively. In the analysis for atherosclerotic plaque, a significant association was found with age ≥ 40 years, the OR being 3.61 (CI 95% 1.03 – 12.63; p = 0.044).

Age and duration of illness were associated with CIMT in this research, similar to the findings in other studies.[17-21] Atherosclerosis is a chronic, continuous process which begins at a young age and grows with age. CIMT in the healthy population usually increase with age.[22] Age is a primary factor that determines the extent of atherosclerosis. Longer an individual suffers from RA, more severe is the atherosclerosis compared to patients of the same age but earlier in the course of the disease. This finding is similar to that reported by Rincon et al.[23]

Hypertension is a traditional predicting factor, significantly associated with atherosclerosis and atherosclerotic plaque formation, OR 4.99 (CI 95% 1.15 – 21.16; p = 0.031) and 3.96 (CI 95% 1.15 – 13.57; p = 0.029), respectively. However a significant association between hypertension and CIMT was not found in the study by Gonzales-Juanatey.[20] On the other hand, Roman MJ showed that in RA patients, atherosclerosis is associated with age, hypertension status, and use of TNF alpha inhibitors.[19] In this study, hypertension was a significant risk factor for atherosclerosis and atherosclerotic plaque formation that can be changed and treated.

Type 2 Diabetes Mellitus was not a predicting factor for the occurrence of atherosclerosis and atherosclerotic plaques in this research. Similarly, MJ Roman, YB Park, and Ahmed also reported the same results.[17,19,21] Different population, genetics, background, RA diagnostic criteria, and also atherosclerosis and atherosclerosis plaque diagnostic critera may cause discrepancy between our result and the others study result.

Dyslipidemia isn't a predicting factor of atherosclerosis and atherosclerosis plaque in this study. Similarly with YB Park and MJ Roman study.[17,19] A complex relationship between dyslipidemia, inflammation, and RA may be the reason underlying the lack of a significant association between dyslipidemia and atherosclerosis in this research, other than the difference in population, RA diagnostic criteria, and method of atherosclerosis examination.

Smoking is a traditional predicting factor for the occurrence of atherosclerosis. In addition, it causes more severe joint damage in RA. However, in this research smoking was not significantly associated with atherosclerosis. There is a need for more subjects who have a smoking habit to correctly identify the role of smoking as the predicting factor for atherosclerosis and atherosclerotic plaques. The study by MJ Roman also reported smoking as a significant predicting factor for atherosclerotic plaques.[19]

The median BMI in this research was 23.9 kg/m$^2$(SE 4.4). Obesity (BMI ≥ 25 kg/m$^2$) was not significantly associated with the occurrence of atherosclerosis in this research. This finding is in accordance with the study by Kremer et al.[24] Different from the common population, RA patients with low BMI (< 20 kg/m$^2$) had a higher risk for cardiovascular death compared to non-RA patients with normal BMI. Moreover, in RA, BMI has a paradoxical effect on mortality. Patients with BMI ≥ 30 had lower mortality rate (1.7 deaths / 100 individuals/year) compared to patients with BMI < 20 (10.5 deaths/ 100 individuals/year).[25] More severe the inflammation appears to be correlated with more severe cachexia that is correlated with increase morbidity rate.

Anti-CCP antibodies were found in 33 subjects (38.4%) in this study. The presence of anti-CCP antibodies was not significantly correlated with the occurrence of atherosclerosis, but the association with atherosclerotic plaque was significant, with OR 3.2 (CI 95% 1.1 – 9.2; p = 0.029). The significant association between anti-CCP with atherosclerotic plaque formation was also reported by Lopez FJL, et al where RA patients with positive anti-CCP antibodies (> 25 unit/mL) had higher myocardial ischemia (6.5% vs. 2.6%; OR 2.56, CI 95% 1.17 – 5.56) and mortality rates (11.2% vs. 6.8%; OR 1.72, CI 95% 1.01 – 2.91) compared to RA patients without anti-CCP antibodies. They demonstrated an association between anti-CCP antibodies of patients with RA and the presence of coronary heart disease independent of traditional cardiovascular risk factors. Their report revealed an underlying autoimmune inflammatory disorder affecting not only the development of articular RA manifestations, but also the cardiovascular comorbidity of RA.[26]

Another research in the Rheumatology Clinic at RSCM by Yuliani and Manuaba reported the prevalence of anti-CCP antibodies at 60.4% (91 subjects) and 56% (46 subjects), respectively.[27,28] This difference may be attributed to the difference in population, RA diagnostic criteria, and method of examination.

The prevalence of antioxidized-LDL antibodies in this research was 61.6% (53 out of 86 subjects). A significant association between anti oxidized-LDL antibodies with atherosclerosis or atherosclerotic plaque formation was not found. In contrast, Ahmed et al, reported that patient age, CRP, and Ox-LDL antibodies were independent risk factors of atherosclerosis.[21] This difference may be caused by the variation in atherosclerosis and atherosclerotic plaque criteria and definition, as well as the method of examination.

Radiology examination score in a cross sectional research describes the severity of joint damage occurring in RA at a specific point of time. In this research, a median Sharp van Heidje score of 28 and 40 for patients with and without atherosclerosis, respectively; and 31 and 40 for patients with and without atherosclerotic plaques, respectively. The differences were not statistically significant. The complex interaction between inflammation, joint damage, and occurrence of atherosclerosis may underlie this result. Similarly, Gonzales-Juanatey et al, did not find a significant association between joint damage (using the Larsen score) with carotid CIMT and carotid plaques.[29]

Multivariate analysis by logistic regression testing allowed the construction of a scoring system which calculates the probability of atherosclerosis and atherosclerotic plaque formation for each score. The prediction score of 0, 1, 2, 3, and 4 are associated with a 4%, 14%, 36%, and 87% probability of developing atherosclerosis, respectively. On the other hand, the score 0, 1, 2, and 3 are associated with a 7%, 20%, 47%, and 76% probability of developing an atherosclerotic plaque, respectively.

Based on the prediction scores for atherosclerosis and atherosclerotic plaque formation, the researchers categorized the prediction scores into low, moderate, and high. For the atherosclerosis prediction score 0 – is low risk with a probability of up to 14% for the occurrence of atherosclerosis (CIMT ≥ 1.0mm). A score of 2 with a 36% probability of developing atherosclerosis is categorized as moderate risk. Further, a score of 3 – 4 are categorized as high risk, with a 66% to 97% risk of developing atherosclerosis. For patients with moderate risk, the researchers recommend CIMT examination to determine the presence of thickening of the tunica intima. For high risk patients, primary prevention of atherosclerosis complications and cardiovascular events, without CIMT examination is recommended (Table 11).

Similarly, there is the prediction scores for the development of atherosclerotic plaques. A score of 0 is considered as low risk with a 7% probability of atherosclerotic plaque. A score of 1 with a 20% probability of atherosclerotic plaque formation is considered as moderate risk, and the researchers suggest CIMT measurement for these patients. Further, a score of 2 – 3 is considered as high risk with at least a 47% probability of developing atherosclerotic plaques. In patients with high risk, primary prevention is recommended without the need for CIMT examination (Table 12).

**Table 9.** Recommendations Based on Atherosclerosis Prediction Scores

| Score | Risk | Probability of Atherosclerosis | Recommendation |
|---|---|---|---|
| 0-1 | Low | 14 % | Observation |
| 2 | Moderate | 36 % | CIMT Examination |
| 3-4 | High | 66 – 87 % | Primary Prevention |

**Table 10.** Recommendations Based on Atherosclerotic Plaque Prediction Scores

| Score | Risk | Probability of Atherosclerotic Plaques | Recommendation |
|---|---|---|---|
| 0 | Low | 7 % | Observation |
| 1 | Moderate | 20 % | CIMT Examination |
| 2-3 | High | 47 - 76 % | Primary Prevention |

Internal validation of this predictive study was conducted using the Bootstrapping method in the statistical software, SPSS. Following 1000 times of sample repetition, the Hosmer-Lameshow value for atherosclerosis and atherosclerotic plaque formation were 0.838 and 0.956, respectively. Both of the p values were > 0.05, thus it may be assumed that the internal validation of this research is good, for the prediction factors of atherosclerosis and atherosclerotic plaque formation.

For external validation, a multicenter research must be conducted with a similar design on the RA population in a different location. The aim of performing a multicenter study is to identify the inference and generalization ability of this study to RA patients in Indonesia, thus allowing the construction of more definite suggestions and recommendations.

Currently, to the researchers' knowledge, this is the first study which focuses on identifying the relationship between the predicting factors, including the demographic (age and duration of illness), clinical (presence of hypertension, diabetes mellitus, dyslipidemia, and obesity), laboratory (presence of anti-CCP and antioxidized-LDL antibodies), and radiology variables (Sharp van Heijde Score) with the occurrence of atherosclerosis and atherosclerotic plaques, identified by CIMT examination as the surrogate marker, by multivariate analysis among the RA population in Indonesia. The results of this research, obtained by multivariate analysis, may be used as the background for more developed research to determine the relationship or association between the independent and dependent variables (atherosclerosis and atherosclerotic plaques), using this research design which is more simple and focused. It is recommended for further research to examine and further identify the role of those significant factors, and to focus on the relationship between hypertension and anti-CCP antibodies with atherosclerosis and atherosclerotic plaque formation.

The results of this study hints on the possible role that anti-CCP antibodies, an important and relatively novel serology analysis in Indonesia, may play in the formation of atherosclerosis and atherosclerotic plaque formation. The significant association between the presence of anti-CCP antibodies and atherosclerotic plaque formation indicates the role of autoimmunity in RA, atherosclerosis, and atherosclerotic plaque formation. The results of this research serve as evidence to the role anti-CCP antibodies in the development of subclinical atherosclerosis and ischemic heart disease in RA patients.[26,29]

For clinicians who deal with RA patients on a regular basis, the results of this research provides a screening and stratification tool for RA patients and their probability of developing atherosclerosis and atherosclerotic plaques.

The cross sectional design of this study does not allow a cause-and-effect analysis of the predicting variables and the outcomes, atherosclerosis and atherosclerotic plaques. Further research with a cohort design is required to clarify the cause and effect relationship between the predicting variables with atherosclerosis and atherosclerotic plaques.

Smoking was not analyzed as a variable because only 1 patient was a smoker. However, smoking has been proven and is known to be an important predicting factor of atherosclerosis and atherosclerotic plaque formation in the non-RA population. The role of smoking as a predicting factor could not be analyzed in this study, thus smoking should be considered in the generalization and inference of the results obtained in this study. The researchers recommend clinical judgment, still more important than the scoring system constructed from this research.

Predicting model or scoring system obtained from this research does not analyze the duration of hypertension, diabetes mellitus, or quantity/length of time of smoking history. This research did not consider the therapy or drugs/combination of DMARDs or other medications such as anti-hypertensives or statins being consumed or have been consumed, which may affect the occurrence of atherosclerosis and/or atherosclerotic plaques. Ultrasound and radiology examinations for atherosclerosis plaque and Sharps van Heidje score was done by one examiner respectively for all subjects.

**Conclusion**

The proportion of atherosclerosis and atherosclerotic plaques among RA patients was 47.7% and 29%, respectively. Age ≥ 40 years, hypertension, and duration of illness ≥ 24 months are, in order, significant predicting factors for the development of atherosclerosis in RA patients. Hypertension, Anti-CCP status, and age ≥ 40 years are, in order, the predicting factors for the development of atherosclerotic plaques in RA patients. Regarding this research, there are several recommendations for researchers, clinicians, and policy makers. First, further research is required, using a prospective multicenter design with more detailed categorization (age; duration of illness; length of time since hypertension and diabetes mellitus diagnosis; quantity and types of medications being consumed, etc) for the external validation and to clarify the relationship between the predicting factors and the occurrence atherosclerosis and atherosclerotic plaques among RA patients in Indonesia. For clinicians and other medical professionals who work with RA patients, and the patient's family members should consider patient age, hypertension, duration of RA disease, and anti-CCP status in the management of RA to reduce mortality due to cardiovascular events. For policy makers such hospital directors, health ministers, and professional organizations such as Indonesian Doctors Association and The Indonesian Society of Internal Medicine to consider factors such as patient age, hypertension, duration of RA disease, and anti-CCP status when constructing the standard operating procedures, clinical practice guidelines, or medical treatment guidelines for the management of RA, to increase the quality of patient treatment; and to allow the optimal, appropriate, and cost-effective use of resources.

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# Correlations between osteoartritis grading in femorotibial joint (kellgren lawrence) with cartilage defects grading

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**Abstract**

**Background :** Osteoarthritis (OA) is the most common chronic rheumatic diseases that causing pain and disability. The imaging of knee OA were found in 15,5% men and 12,7% women of Indonesia population. Radiography is still used as a standard modalities in assesing OA progression, and Kellgren-Lawrence scale (KL) is the most common measurement used by clinicians. Superficial cartilage degradation is the first sign of OA, the early detection of the superficial cartilage degradation is very important for diagnosis. Our study was established to assess the correlation between OA grading in femorotibial joint examined by standard Kellgren-Lawrence scale (KL) measurement with cartilage defects examined by ultrasound.

**Methods :** Observational analytic study with cross sectional and consecutive sampling was performed. Rank Spearman test for correlation of OA grading, cartilage defect, BMI and joint malalignment. McNemar test for correspondence between the location of the narrowing of the femorotibial joint and location of cartilage defects.

**Result :** Correlation of OA grading of femorotibial joints (KL) with cartilage defects grading on ultrasound resulted r $=0.459$, $p<0.05$; correlation of OA grading of femorotibial joints (KL) with BMI or joint malalignment resulted $p>0{,}05$; correlation of cartilage defect grading with BMI or joint malalignment also resulted $p>0.05$. McNemar test for location of the narrowing of the femorotibial joint with location of cartilage defects on ultrasound resulted $p = 1.00$, $k = 0.714$. There was a significant positive correlation of OA grading of femorotibial joints (KL) with cartilage defects grading on ultrasound. There was no significant correlation between OA grading of femorotibial joints (KL) with BMI and joint malignment, and no significant correlation between cartilage defects grading with BMI and joint malalignment. There is a correspondence between the location of the narrowing of the femorotibial joint with location of cartilage defects on ultrasound.

**Conclusion:** For assesing the grade of osteoartritis, cartilage defect grading and assesment by ultrasound can be used as an alternative to X-Ray Kellgren-Lawrence scale (KL) measurement.

**Keywords :** femorotibial joint, cartilage defects grading, osteoartritis grading examination, BMI, joint malalignment.

## Background

Osteoarthritis (OA) is a chronic rheumatic diseases most frequently encountered and causes pain and disability. It is a degenerative joint disease, which encountered the joints that support the body weight.[1-3] Some special characteristics that could be found in OA, include: the erosion of cartilage, bone hypertrophy (osteophytes), subchondral sclerosis, as well as biochemical and morphological changes in the synovial membrane and joint capsule.[4]

The prevalence of knee OA in Indonesia reached 15.5% in men and 12.7% in women. [5] In Prof. Dr. R. D. Kandou Hospital, during the month of March 1994 until November 1995, the prevalence of OA reached out 36.81%. OA is the highest cases (37%) among all arthritis cases in our hospital, and knee OA account for 97% of all OA patients. [6]

The knee joint has three compartments, among others: femorotibial lateral, femorotibial medial and femoropatela.[3] Process biochemistry involving cartilage, bone and synovial can damage all compartments of the knee joint.[3,7] Some risk factors of OA, include age, heredity, joint *malalignment,* obesity, metabolic diseases and trauma to the joint. Each factor contributes to the pathogenesis of early and advanced OA disease.[3,]

Radiography is still the standard assessment of OA progression, and scale of Kellgren-Lawrence (KL) is the most common radiographic modality used by clinicians.[8-10] However, ultrasound can be used to detect an early manifestation of osteoartritis abnormalities in patients with osteoarthritis.[8] OA disrupts the collagen network, declines the proteoglycans, increases the water content, and results mechanical changes in joint cartilage.[11] Trauma to the collagen network leads the development of an advanced OA. [12] Superficial degradation of cartilage is an early sign of OA. Therefore, the early detection of the superficial cartilage degradation is very important for diagnosing OA. [13] If the early changes can be diagnosed properly, disease progression can be declined with medication intervention and lifestyle changes.[14] Therefore, we aim to assess the correlation between OA grading in femoropatella joint by Kellgren Lawrence scale measurement with cartilage defects grading by ultrasound examination.

**Methods**

Observational analytic study with crosssectional and consecutive sampling was performed for this study. Data that is analyzed, includes charateristics of subjects (age, level of work, and BMI); OA grading by X-Ray examination; cartilage defect grading by ultrasound assesment. Grading of OA is done using Kellgren-Lawrence (KL) score. Grading of cartilage defect by ultrasound assesment is done using International Cartilage Repair Society classification. Level of work is measured based on Mathenson LN classification. WOMAC score is used to asses any pain, rigidity and disability. Subjects are classified based on Likert scale: (0) no symptoms; (1) mild symptoms; (2) moderate symptoms; (3) severe symptoms; and (4) very severe symptoms. Rank Spearman test are done for assesing the correlation of OA grading with cartilage defect, BMI and joint malalignment, respectively. McNemar test are done to search any correspondence between the narrowing location of the femorotibial joint and the location of cartilage defects.

**Result**

Forty-three samples were included as respondents in this study. Respondents age range from 41 to 77 years old, with an average of 57,8 years old. Portion of group age is dominated by group of 50-59 years old, which account for 17 people (39,5%). Women account for 72,1 % (33 people). Samples grouped as"heavy work", classified by Matheson LN, were as much as 21 people (48.8%). Most BMI value at the level of *overweight* and obesity as much as 22 (51.2%). Characteristics of study subjects, such as: age, weight, job, BMI, OA grading, cartilage defect grading, malalignment, and WOMAC scores can be seen in Table 1.

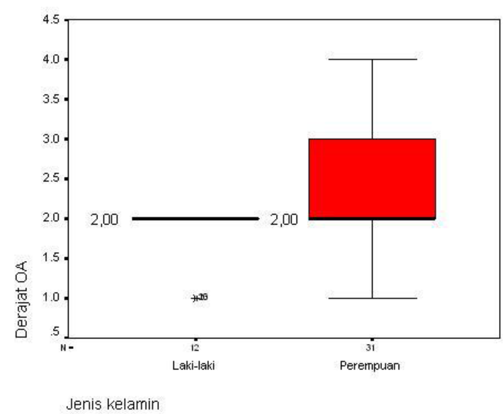
**Table 1** Subjects Characteristics

| Characteristics | Gender N(%) | | Total |
|---|---|---|---|
| | Man | female | N(%) |
| **Age Group** | | | |
| 40-49 | 2 (28.6) | 5 (71.4) | 7 (16.3) |
| 50-59 | 4 (23.5) | 13 (76.5) | 17 (39.5) |
| 60-69 | 3 (21.4) | 11 (78.6) | 14 (32.6) |
| 70-79 | 3 (60.0) | 2 (40.0) | 5 (11.6) |
| **Level of work** | | | |
| Light | 0 (0) | 12 (100) | 12 (27.9) |
| moderate | 7 (33.3) | 14 (66.7) | 21 (48.8) |
| Weight | 3 (50.0) | 3 (50.0) | 6 (14.0) |
| Very heavy | 2 (50.0) | 2 (50.0) | 4 (9.3) |
| **BMI** | | | |
| Normoweight | 6 (28.6) | 15 (71.4) | 21 (48.8) |
| Overweight and obesity | 6 (27.3) | 1 6 (72.7) | 22 (51.2) |
| **OA grading** | | | |
| 1 | 2 (28.6) | 5 (71.4) | 7 (16.3) |
| 2 | 10 (37.0) | 17 (63.0) | 27 (62.8) |
| 3 | 0 (0) | 5 (100) | 5 (11.6) |
| 4 | 0 (0) | 4 (100) | 4 (9.3) |
| **Cartilage defect grading** | | | |
| 0 | 6 (75.0) | 2 (25.0) | 8 (18.6) |
| 1 | 2 (11.8) | 15 (88.2) | 17 (39.5) |
| 2 | 1 (33.3) | 2 (66.7) | 3 (7.0) |
| 3 | 2 (16.7) | 10 (83.3) | 12 (27.9) |
| 4 | 1 (33.3) | 2 (66.7) | 3 (7.0) |
| **Malalignment** | | | |
| Normal | 10 (30.3) | 23 (69.7) | 33 (76.7) |
| Varus | 0 (0) | 3 (100) | 3 (7.0) |
| Valgus | 2 (28.6) | 5 (71.4) | 7 (16.3) |
| **WOMAC score** | | | |
| OA 1 | | | 1.636 |
| OA 2 | | | 1.188 |
| OA 3 | | | 1.265 |
| OA 4 | | | 1.383 |

Normoweight: BMI (18,5-25kg/m$^2$); obesity and overweight: BMI (>25 kg/m$^2$)

Majorly samples have grade 2$^{nd}$ OA, measured in 27 people (62.8%), with the number of women 17 people (63.0%). The median value of the OA grading for both men and women is the same, grade 2, as presented in Figure 1.

**Figure 1** Boxplot OA degrees of subjects by sex.




Analysis of the relationship between OA grading of femorotibial joints with BMI, showed no significant relationship (p> 0.05). The median BMI of samples whose have grade 3$^{rd}$ OA and grade 4$^{th}$ OA were 26.37 kg/m$^2$ and 27.66 kg/m$^2$, respectively, as seen in Table 2.

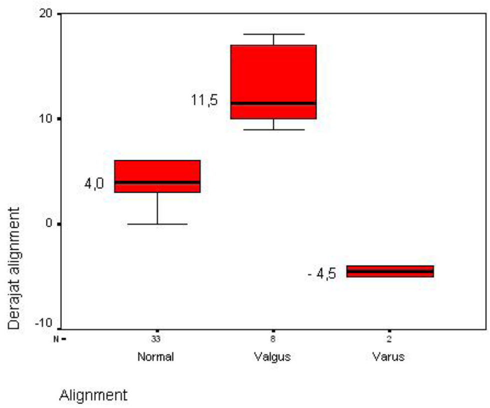
**Table 2** Correlation of femorotibia joint OA grading and BMI

| BMI | OA grading of femorotibia joint | | | | p value |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| 18.5-25 kg/m$^2$ | 4(57.1) | 15(55.6) | 2(40.0) | 0(0) | 0.199 |
| >25 kg/m$^2$ | 3(42.9) | 12(44.4) | 3(60.0) | 4(100) | |

Group as normoweight (BMI 18.5-25 kg/m$^2$) and overweight/obesity (BMI >25kg/m$^2$)

From the measurement of femorotibial angle at the knee joint, samples obtained normal alignment account for 33 joints (76.7%), with median value 4°valgus; valgus alignment account for 7 joints (16. 3%), with median value 11.5°valgus; and varus alignment account for 3 joints (7 .0%), with median value 4.5°varus. The boxplot is shown in Figure 2.

**Figure 2.** Boxplot of femorotibia joints malaligment



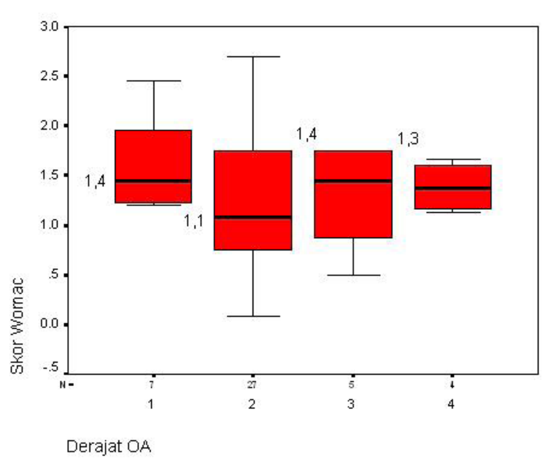

Correlation analysis of OA grading and malignment in femorotibial joints is showed in Table 3. Our study resulted no significant relationship (p> 0.05) between OA grading and malalignment in femorotibial joint. The 1st grade OA have median malalignment value of 6°valgus, the 2nd grade OA have median malalignment value of 5°valgus, 3rd grade OA have median malalignment value of 3°valgus, and the 4th grade OA have median malalignment value of 8.8° valgus.

**Table 3** Correlations OA grading of femorotibia joint with malalignment

| | OA grading of femorotibia joint | | | | *p value* |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Malalignment | 2 (28.6) | 4 (14.8) | 2 (40.0) | 2 (50.0) | 0.311 |
| No Malalignment | 5 (71.4) | 23 (85.2) | 3 (60.0) | 2 (50.0) | |

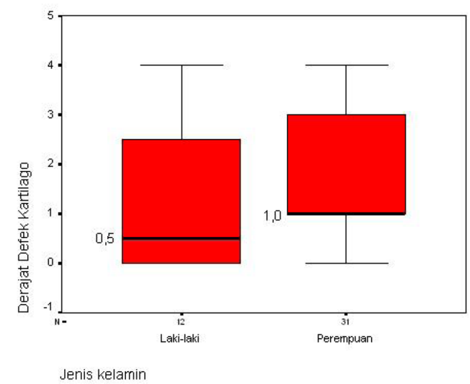
The mean WOMAC score of the samples is classified as mild to moderate class. The median WOMAC score of 1st grade OA, 2nd grade OA, 3rd grade OA, and 4th grade OA are 1.4, 1.1, 1.4 and 1.3, respectively, as shown in figure 3.

**Figure 3** Boxplot of WOMAC scores and OA grading




Most cartilage defects were found in the 1st grade OA, which were examined in 17 subjects (39,5%), and 15 subjects (88,2%) of them were female. The median value cartilage defect degrees for men is 0.5 and for women is 1, as presented in figure 4.

**Figure 4** Boxplot of cartilage defects degrees by sex




BMI had no significant relationship with cartilage defect (p>0,05), as presented in table 4. Subjects with cartilage defect grading as 0 have average BMI of 26,7 kg/m², which classified as overweight. Subjects with cartilage defect grading as second, third, and fourth, have average BMI of 31.6 kg/m²; 26.6 kg /m²; 26.3 kg/m², respectively.

**Table 4** Correlations cartilage defects grading with BMI

| **BMI** | **Cartlage defects grading** | | | | | **p value** |
|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** | |
| **18,5-25kg/m²** | 3(37.5) | 12(70.6) | 1(33.3) | 4(33.3) | 1(33.3) | 0.252 |
| **>25 kg/m²** | 5(62.5) | 5(29.4) | 2(66.7) | 8(66.7) | 2(66.7) | |

The relationship of cartilage defect grading with malalignment showed no significant relationship (p> 0.05), as shown in table 5. The median value of alignment in subjects with no cartilage defect were 6°valgus; in subjects with first grade cartilage defect were 4°valgus; in subjects with second grade cartilage defects were 5°valgus; in subjects with third grade cartilage defects were 3.5°valgus; and in subjects with fourth degree cartilage defects were 0°valgus.

**Table 5** Correlations cartilage defects grading with malalignment

| | **Cartlage defects grading** | | | | | **p value** |
|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** | |
| **Malalignment** | 2(25.0) | 3(17.6) | 1(33.3) | 3(25.0) | 1(33.3) | 0.954 |
| **No Malalignment** | 6(75.0) | 14(82.4) | 2(66.7) | 9(75.0) | 2(66.7) | |

The thickness of the cartilage had an average value of 0.18 cm on the medial side; 0.20 cm on the trochlear, and 0.17 cm on the lateral side. The median value of cartilage thickness of KL 3 was 0.20 cm, 0.15 cm, and 12.09 cm for medial side, trochlear, and lateral side, respectively. The median value of cartilage thickness of KL 4 at medial side was 12.05 cm, the trochlear was 0.26 cm, lateral side was 0.19 cm.

We found a strong correlation between the location of cartilage defect assesed by USG and the location of narrowing femorotibia joint measured by x-ray imaging, McNemar test resulted p>0.05 and kappa scored 0.714, as seen in table 6.

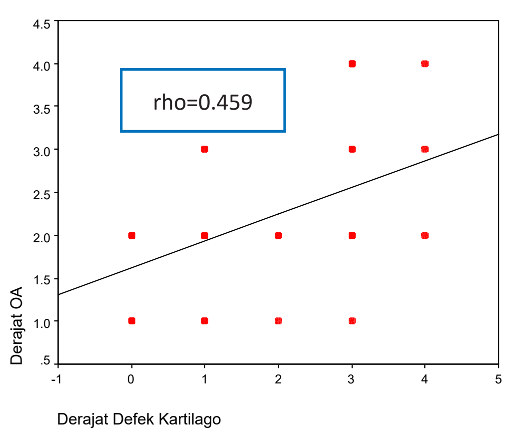
**Table 6** Allocation of cartilage defect (by USG) and narrowing femorotibia joints (by X-Ray)

| Location narrowing on X-Ray medial | | Location defect Ultrasound lateral | |
|---|---|---|---|
| **Medial** | N (%) | 5 (62.5%) | 1 (12,5%) |
| **Lateral** | N (%) | 0 (0%) | 2 (25%) |

p value=1,000; kappa=0,714

Rank Spearman test for OA grading of femorotibial joints (KL) with cartilage defects on ultrasound showed a significant positive correlation with *p* value= 0.002 with correlation coefficients (rho)= 0.459. The median value of cartilage defect in first grade OAwas 1, second grade OA was 1, third grade OA was 3, and fourth grade OA 4 was 3, can be seen in Figure 5.

**Figure 5.** Scatter Graph of femorotibia Joint (KL) OA Grading and Cartilage Defects.




## Discussion

In this study the number of women is more than men. This is consistent with the fact that women have risk factors of knee OA rather than men. M. Blagojevic, et al. (2010), performed a cohort, case-control study stated that women are more susceptible than men.[15] Yuqing Zhang, et al. (2004) suggested that the long squat activity is a strong risk factor of the occurrence of knee OA in old people.[16]

Analysis correlations of OA grading in femorotibial joints and BMI have no significant relationship (p> 0.05). Velandai, et al. in 2005 with population based study stated that women in age ≥ 55 years tend to be exposed more severe than men.[17] While, Shiozaki H, et al. study, a 14 years longitudinal study (1979-1993) in 1191 women concluded that patients with overweight and obesity at the initial survey may have higher risk to developed OA and higher risk of knee OA progression if OA has developed before.[18] Reijman M (2006) study, concluded that higher BMI increases the incidence of knee OA (OR 3.3) and is associated with knee OA progression (OR 3.2) .[19]

Subjects mostly have normal femorotibia alignment, 33 of 43 joints (76.7%); and Varus and valgus account for 10 joints (23.3%). However, malalignment and OA grading have no significant correlation (p> 0.05). In the other hand, Sharma L, et al. (2010) cohort study mentioned that the knee joint with varus and valgus alignment have increased OA progression.[20] Moreover, Teichtahl AJ, et al. (2006) study stated that varus alignment associated with the risk of narrowing of the medial compartment joints (p <0.001) and valgus alignment associated with the risk of narrowing of the lateral compartment joints (p <0.001).[21] In addition, joints malalignment can also be affected by disease duration and type of work. Unfortunately, we have not performed any analysis of joint malalignment in patients based on disease duration and type of work.

In this study, the degree of pain, stiffness and resistance activity in OA grade 1 is higher than OA grade 2,3, and 4. This study is consistent with Link TM, et al. (2002) and Cubukcu D, et al. (2012) that stated no significant relationship between KL and WOMAC score (p> 0.05).[10,22] Dieppe PA and Lohmander S (2005) mentioned that the pain is influenced by many factors, such as biochemical pathways (cytokines, proteases), location and severity of OA, as well as psychosocial and socioeconomic factors ie. comorbid diabetes, hypertension, coronary heart disease, kidney failure, gastrointestinal bleeding, depression, impaired physical and obesitas.[23] While, Brandt KD, et al. (1998) told that pain is caused by few sources, include periosteal stretching, osseous hypertension, microfracture subchondral, ligament strain, enthesopathy, bursitis, hypertension intraarticular, instability of the joint capsule and ischemia sinovium.[24] Additionally, some of our subjects had received physiotherapy and analgesics which might influence the pain measurement.

In this study, most subjects were suffered by first grade cartilage defects (39.5%). Obesity and joints abnormalities are factors that influence abnormal pressure on the joints and lead to cartilage damage. In this study, we found no significant relationship between cartilage defects grade with BMI and joint malalignment (p> 0.05). Consistently with Tuck Davies, et al. (2008) study, which mentioned that BMI was not associated with cartilage defects (p = 0.60 for cartilage defect in the medial tibiofemoral and p = 0.92 for the lateral tibiofemoral cartilage defects).[25] Janakiramanan N, et al. (2006) concluded that the change of 1° towards genu valgum in patients with osteoarthritis would decrease the risk of medial tibial cartilage defects (OR 0.86), but increase the risk of lateral tibial cartilage defects (OR 1.06).[26]

Thickness of the cartilage on the medial side is 0.18 cm, trochlear side is 0.20 cm and the lateral side is 0.17 cm. However, Iagnocco A (2010) study stated that the average of cartilage thickness is 3 mm.[8] Moreover, measurement of cartilage thickness in this study is also different from the research conducted by Kazam, et al. in USA (2011). In that study, the average thickness on medial side was 0.23 cm, trochlea side was 0.31 cm and the lateral side was 0.22 cm. Differences in cartilage thickness can be caused by the different posture of the USA and Indonesian people.[27]

McNemar test are based on the suitability of the results of the examination with p> 0.05, the kappa test obtained value of k = 0.714 which showed high conformity between cartilage defects locations on USG and narrowing of femorotibial joints on X Ray. Spearman Rank test between OA grading on femorotibial joints (KL) by X-ray with cartilage defect grading on ultrasonography showed a significant positive correlation with p value 0.002 with correlation coefficients (rho) 0.459. The median value in cartilage defect of the first and second grade OA were 1, while the median value of the cartilage defect of the third and fourth degree were 3. This is consistent with Link TM, et al (2002) cross-sectional study that assessed the correlation of KL with cartilage lesions on MRI. That study concluded that the degree of cartilage lesions on MRI increases with increased KL scores (rho = 0:55, p <0.01).[10]

## CONCLUSION

There is a significant positive correlation between OA grading in femorotibial joints (KL) with cartilage defects grading assesed by ultrasonography. It can be implied that a cartilage defect grading by ultrasonography has the same diagnostic value with an X-ray imaging to measure OA grading by KL scoring system. Cartilage defects in the knee joint can affect radiographic changes. The osteophytes trigger defects in cartilage though improved power transmission and cartilage defect causes a narrowing of the joint.[28]

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# 24-Hour Proteinuria Weakly Correlated with Estimated Glomerular Filtration Rate in Lupus Nephritis Patients

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**Abstract**

**Background:** Lupus Nephritis (LN) is still the most frequent complication in Systemic Lupus Erythematous (SLE) patients which causing the major and significance morbidity and mortality. Proteinuria and Glomerular Filtration Rate (GFR) serves as objective and routine examinations to assessrenal function. 24-hour proteinuria still regarded as gold standard to quantify amount protein in urine. Estimated GFR (eGFR) is preferably used due its convenient. On the hand, estimated GFR (eGFR) is preferably used due its convenient. However, both of them should be measured in order to determine renal progression and prognosis. Only few studies have been conducted to find out the correlation between 24-hour proteinuria and eGFR in lupus nephritis patients as both of them serve as potential marker in progression of renal involvement. This study addressed to find out correlation between 24-hour proteinuria and eGFR in lupus nephritis patients.

**Method:** Analytic-correlation study with cross-sectional approach at Dr. Hasan Sadikin Hospital, Bandung was done. Secondary data was used and paralleled with previous study entitled "Correlation of Random Urine Protein Creatinine (P-C) Ratio with 24-Hour Protein Urine in Lupus Nephritis Patients" carried out from October to December 2014.Correlation coefficient was analyzed by *Spearmans*' correlation test.

**Results:** Forty five samples were obtained based on inclusion criteria. *Spearmans*' correlation test revealed non significant and very weak correlation between 24-hour proteinuria and eGFR ($r=-0.095$) with $p>0.05$.

**Conclusion:** The 24-hour proteinuria and eGFR are weakly correlated. Despite the weak correlation, these examinationsshould be considered as important markers to monitor prognosis of renal involvement in lupus nephritis patients

**Keywords:** Estimated glomerular filtration rate (eGFR), Lupus Nephritis (LN), Proteinuria, Systemic Lupus Erythematosus (SLE).

## Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with multisystem clinical manifestations and complications ranged from decreasing quality of life until death.[1,2]Around 60% of SLE patients' will suffer of renal involvement, lupus nephritis (LN), which significantly increase their morbidity and mortality.[3,4] Mortality rate in SLE patient with LN is8-fold higher than SLE patients without renal involvement.[5]Around 17 % LN patients will develop chronic kidney disease (CKD) or terminal stage of renal failure. This condition caused the requirement of a lifetime hemodialysis or expensive renal transplantation.[6,7]

Most of LN are clinically asymptomatic due to slow declining progression ofrenal function.[8] Both of Glomerular Filtration Rate (GFR) and proteinuria are currently used to assess kidney function.[9] Estimated GFR (eGFR) is preferably used instead of inulin clearance due its convenient and strong correlation with GFR.[9,10] On the other hand, proteinuria is also a strong independent predictor of the declining GFR and serves as prognostic factor in chronic kidney disease.[3,11] The 24-hour urine collection is still regarded as gold standard of proteinuria measurement although alternative methods are already proposed.[11] Several studies revealed proteinuria associates with the fasten progression of renal function declining and serves as an important marker in the etiology of lowered eGFR.[12] In addition, patients with heavy proteinuria and normal eGFR have higher mortality rate compared to those with low or no proteinuria and low eGFR.[13] Hence, it is important to assess both proteinuria and eGFR in patients with renal dysfunction, especially in lupus nephritis where renal flare might be occured anytime.[4] Only few studies have already carried out to discover the correlation of 24-H proteinuria and eGFR in LN patients.[14] This study was addressed to find out the correlation between 24-hour proteinuria and eGFR in lupus nephritis patients.

## Method

We conducted an analytic-correlative study with cross-sectional approach at Dr. Hasan Sadikin Hospital, Bandung. This study used secondary data and paralleled with previous study entitled "Correlation of Random Urine Protein Creatinine (P-C) Ratio with 24-Hour Protein Urine in Lupus Nephritis Patients"[15] carried out from October to December 2014. This study has alreadyapproved by Health Research Ethics Committee in Hasan Sadikin General Hospital.

The subjects of this study were patients who had been diagnosed as lupus nephritis based on American College of Rheumatology, came to

Rheumatology Wards in Hasan Sadikin General Hospitalon October to December 2014 have regular control. Minimum sample required in this study is 141. However, total sampling method used because only 45 data were available. Eligible sample selected based on inclusion criteria: available data of complete laboratory test of 24-hour proteinuria and eGFR; and exclusion criteria: patients who were having menstruation, and suffered from other glomerulopathies, urinary tract infection, and inadequate 24-hour urine.[15]

Data analysis includes: sample demographic charactertics, such as age, gender, and duration of having SLE; proteinuria measured by 24-hour urine collection method; and eGFR calculated by *Cockcroft-Gault*[4]. Proteinuria was classified based on protein urine excretion level into 3 groups (minimal, moderate or non nephrotic, heavy or nephrotic). eGFR was classified based on "CKD prognosis on Kidney Disease: Improving Global Outcomes (KDIGO)" into 6 groups (Grade 1,2,3a,3b,4,5).

Distribution of the data was analyzed by *Shappiro-Wilk test*. Furthermore, 24-hour proteinuria and eGFR analyzed by *Spearmans* correlation test and p<0.05 considered statistically significance.[16] Statistical analysis was performed using statistical analysis software.

**Result**

This study involved 45 persons. The subjects' characteristics are presented in Table 1.

**Table 1** Characteristic of the samples

| Variable | Result (45 subjects) |
|---|---|
| Age (years, Mean± SD) | 32,23 ± 10,95 |
| Gender,n(%) | |
| • Female | 44 (97.8) |
| • Male | 1 (2.2) |
| Duration SLE, n(%) | |
| • < 1 year | 10 (22.2) |
| • ≥ 1 year | 35 (77.78) |

The 24-hour proteinuria was classified based on amount of protein urine excretion each into different groups as shown in Table 2.

**Table 2** Characteristic of 24-hour Proteinuria

| Variable | Median | Range |
|---|---|---|
| 24-hour proteinuria (mg/24 hours) | 387,5 | 52,90-5800 |
| Classification based on protein urine excretion | N (%) | |
| • Minimal | 31 (68.9) | |
| • moderate | 12 (26.7) | |
| • Nephrotic or heavy | 2 (4.4) | |

Minimal= proteinuria <1000 mg/24 hours; moderate= non nephrotic, proteinuria 1000-3500 mg/24 hours; heavy= nephrotic, proteinuria >3500mg/24 hours

The eGFR was classified based on grading of CKD in KDIGO guideline each into different groups as shown in Table 3.

**Table 3** Characteristic of Estimated Glomerular Filtration Rate (eGFR)

| Variable | Median | Range |
|---|---|---|
| Estimated Glomerular Filtration Rate (ml/min) | 89,360 | 11,66-268,68 |
| KDIGOs' classification of CKD | N (%) | |
| • Grade 1 | 22 (48,9) | |
| • Grade 2 | 16 (35,5) | |
| • Grade 3a | 2 (4,4) | |
| • Grade 3b | 4 (8,9) | |
| • Grade 4 | 0 (0) | |
| • Grade 5 | 1 (2,2) | |

Grade 1= normal/high, eGFR ≥ 90 ml/min; Grade 2= Mildly decreased, eGFR 60-89 ml/min; Grade 3a= Mildly to moderately decreased, eGFR 45-59 ml/min; Grade 3b= Moderately to severely decreased, eGFR 30-44 ml/min; Grade 4= Severely decreased, eGFR 15-29 ml/min; Grade 5= Kidney failure, eGFR ≤15 ml/min.

The 24-hour proteinuria was classified based on protein urine excretion and cross tabulated with eGFR based on KDIGO classification were presented in Table 4:

**Table 4** Cross tabulation frequency of 24-hour proteinuria and eGFR

| 24-hour Proteinuria (mg/24 hours) | eGFR ml/min [n(%)] KDIGO | | | | | |
|---|---|---|---|---|---|---|
| | G1 | G2 | G3a | G3b | G4 | G5 |
| Mild | 16 (35.8) | 12 (26.8) | 1 (2.2) | 2 (4.4) | 0 (0.0) | 0 (0.0) |
| Moderate | 4 (8.8) | 4 (8.8) | 1 (2.2) | 2 (4.4) | 0 (0.0) | 1 (2.2) |
| Heavy | 2 (4.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Total | 22 (49.0) | 16 (35.6) | 2 (4.4) | 4 (8.8) | 0 (0.0) | 1 (2.2) |

24H-Proteinuria: Minimal= proteinuria <1000 mg/24 hours; moderate= non nephrotic, proteinuria 1000-3500 mg/24 hours; heavy= nephrotic, proteinuria >3500mg/24 hours;
eGFR: Grade 1= normal/high, eGFR ≥ 90 ml/min; Grade 2= Mildly decreased, eGFR 60-89 ml/min; Grade 3a= Mildly to moderately decreased, eGFR 45-59 ml/min; Grade 3b= Moderately to severely decreased, eGFR 30-44 ml/min; Grade 4= Severely decreased, eGFR 15-29 ml/min; Grade 5= Kidney failure, eGFR ≤15 ml/min.

Graph of analytical correlation test between 24-hour proteinuria and GFR used *Spearmans*' correlation test was shown in Figure 1.

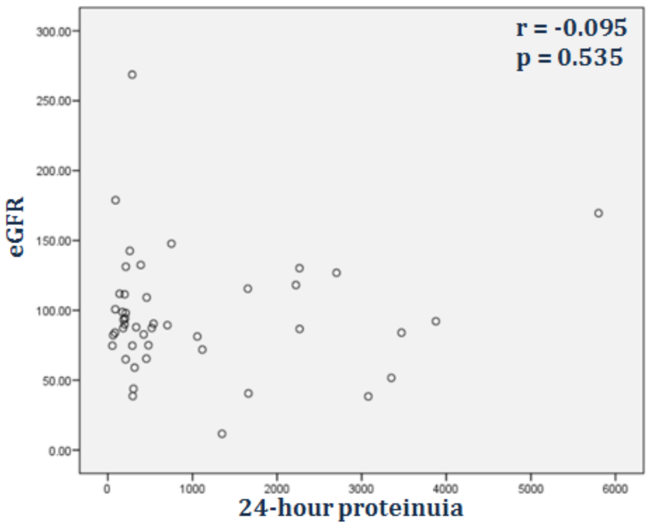


**Figure 1** Correlation between 24-hour Proteinuria and eGFR

**Discussion**

Our study reveals female has higher prevalence (97.8% of patients) than the male. Most of subjects (77.78%) have been diagnosed as SLE for more than 1 year. Most of subjects have mild proteinuria following by higher eGFR. We found a very weak correlation between 24-hour proteinuria and eGFR.

Proteinuria serves as an important marker in diagnosing lupus nephritis, when renal biopsy can not be performed.[7,9] Most of the proteinuria was found with the range from moderate to heavy nephrotic level.[9,17] So did in our study, which reveals 31.1% patients who had moderate to heavy proteinuria. This result was also in line with the previous study conducted by Sircar, et al., in which revealed 42% patients with nephrotic proteinuria.[14]

Glomerular Filtration Rate is a gold standard measurement of renal function, particularly to determine CKD grade and prognosis.[18,19]However, our study used eGFR as an alternative method of GFR measurement, since it is more convinient and most data had not provided the GFR measurement.[10] Our study revealed 84.4% of patients have low risk on CKD based on KDIGO classification G1 and G2. It reflected that most patients are well treated that resulted a significant renal improvement. Chronic kidney disease could not be diagnosed in this study, since the measurement of GFR was only taken once, whereas it requires, at least, 3 month to monitor eGFR progression to be termed as chronic kidney disease. Unfortunately, some of our subjects were also encountered declining of renal function even though receiving adequate therapy. It requires further analysis to determine any factors that affected to this result.

Both of proteinuria and eGFR are routinely measured to monitor renal function, specifically in patients with high proteinuria and low eGFR level.[13] This study reveals that most of patients who has mild proteinuria level exhibited normal or higher eGFR, as previously mentioned. However, there were 4.4% of patients had heavy proteinuria encountered with normal or higher eGFR based on KDIGO. This condition is diagnosed as membranous lupus nephritis, by considering the proteinuria level rather than GFR.[9] Study conducted in Eastern India revealed a significant and negative weak correlation between proteinuria and GFR.[14] The negative correlation result between the variables reflected higher level of proteinuria may lowered eGFR, hence proteinuria becomes a potential marker to determine renal dysfunction.[3,13]However, our study revealed no-significant and very weak correlation between 24-hour proteinuria and eGFR. We suggested that the no-significant and weak correlation results were impacted by the treatment gotten by each patients thus most of patients had already shown renal improvement. Furthermore, this result also implicated correlation between 24-hour proteinuria and eGFR is promising markers in order to assess kidney function as both of them serve as routine and objective examination in lupus nephritis patients.[3,9,11]

Several studies have already conducted to discover the correlation between proteinuria and GFR shown various result.[18-21] They reported proteinuria plays a significant role in declining GFR, and both of them should be measured to assess renal function.[12,13,20] Proteinuria can be markers for both glomerular dysfunction and renal disease progression.[21] However, this study reveals very weak correlation between 24-hour proteinuria and eGFR in lupus nephritis. Most of patients have normal or higher eGFR and mild proteinuria even though diagnosed as lupus nephritis. This result most likely confounded by treatment undergone by the subjects, hence most of them show renal improvement based on proteinuria and eGFR level.

Limitations of this study are samples only taken in once and minimum samples are not fulfilled. Every patients involved in this study had already received therapy that becomes potential confounding in this study. So, we cannot provide baseline data of patients before undergoing therapy.

**Conclusion**

Based on this study, it is concluded there is a very weak correlation between 24-hour proteinuria and eGFR in lupus nephritis patients.Despite the weak correlation, these examinationsshould be considered as important markers to monitor prognosis of renal involvement in lupus nephritis patients. Further studies should be reattempted to evaluate these results by taking the sample periodically in order to monitor eGFR, considering its convenient and cost-effective method.

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# Effect of vitamin D supplementation on disease activity (SLEDAI) and fatigue in Systemic Lupus Erythematosus patients with hipovitamin D: An Open Clinical Trial

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**Abstract**

**Background :** Low level of vitamin D impact the disease activity and the degree of fatigue in SLE patients. This study aims to determine the effect of vitamin D supplementation on disease activity and fatigue condition in Systemic Lupus Erythematosus (SLE) patients with hipovitamin D.

**Methods**: We performed an open clinical trial. Subjects were randomized into two different groups (supplementation or placebo) using simple random sampling. The treatment group got vitamin D3 softgel/ cholecalciferol 1200 IU/day or 30 mg/day, while the control group gotplacebo for 3 months. SLEDAI scores and FSS scores were calculated at pre and post treatment.

**Results**: There were 20 subjectsfor supplementation group and 19 subjects in the placebo group. From this study, before and after treatment, we found a significant difference of mean level of vitamin D in supplementation group ($p=0.000$), and no significant difference in patients with placebo ($p=0.427$). Moreover, from the SLEDAI score analysis, observed a significant difference bothin the supplemented group ($p=0.000$) and the placebo group ($p=0.006$). FSS scores significantly different in the supplemented group ($p=0.000$). In correlation test,there was a negative correlation (r=-0763) between vitamin D level and disease activity (SLEDAI), and both showing stastistical significance between thepre supplementation ($p=0.000$) and post supplementation (r=-0846; $p=0.000$). Similarly to the FSS scores, there was a meaningfulnegative correlation ($r=-0.931$, $p=0.000$) between the level of vitamin D with FSS scores pre and post supplementation ($r=-0.911$; $p= 0.000$). Furthermore, there was a significant correlation between disease activity (SLEDAI) pre supplementation with fatigue condition pre supplementation ($r=0.846$; $p = 0.000$) and post supplementation ($r=0.913$; $p= 0.000$).

**Conclusion**: The supplementation of vitamin D 1200 IU per day in patients with SLE improve disease activity and degree of fatigue.

**Keywords:** vitamin D, disease activity, fatigue, SLE

## Background

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects almost every organ in human body. This disease primarily affects women in reproductive age with the female: male ratio 8: 1. Prevalence of SLE has been reportedto be12.2 per 100,000 population with a high mortality and morbidity rate, especially in developing countries. Although 5 years survival rate of patients SLE has increased to 90% at developing countries, but Handono, et al. (2000) showed that SLE patients in Indonesia hadlower life expectancy,with only 70% for 5 years survival rate and 50% for 10 years survival rate.[1]

SLE interferes the autoregulation of the immune system. The role of immune regulation in SLE patients is influenced by the level of vitamin D,[2] it was supported by the results of a study, which found anegative correlation between vitamin D level and disease activity, degree of fatigue, and production of autoantibody.[3] Another study conducted in Indonesia stated that 71% SLEpatients experienced deficiency of vitamin D.[4] This low level of vitamin D may be happened due tosun avoidance because of photosensitivity that result inless sun exposure.[5] Low levelof vitamin D in patients with SLEhasimpacted the clinical condition of the patient, which would certainly affect the disease activity itself.

Fatigue is a serious problem in SLE patients. One study showed that nearly 81% of SLEpatients experienced fatigue, 60% of them had lowsleeping quality.[6] These results were supported by *in vivo* studies in SLE patients which proved that the administration of 1,25 $(OH)_2D_3$ improved the life ofquality of patients, and one of it wasfatique[7]. The presence of fatigue in patients with SLE will lower patients' compliance onthe treatment, and causing negative impact on their social life infamily and community. Therefore, this study is aimed to determine the effect of vitamin D supplementation on the disease activity and fatigue condition in SLE patients with hypovitaminosis D.

## Research Methods

*Study Design*

This was an open label clinical trial with a control (SLE patients that get standard SLE therapeutic and plasebo) to assess the effects of vitamin D supplementation on disease activity and the degree of fatigue in SLE patients with hypovitaminosis D. The study was conducted atoutpatient and inpatient settingsin Rheumatology division of the Department of Internal Medicine Dr. Saiful Anwar Hospital Malang. Research was carried out from January 2013 to December 2013. The study lasted for 3 months for eachpatient.

*Population and Sample Research*

Population in this study was SLE patients who sought treatment from Internal Medicine Deparment Dr Saiful Anwar Hospital within 1 year. Diagnosis was taken based on the ACR criteria 1997. Samples were SLE patients who had vitamin D deficiency and met the inclusion criteria based on the determined time. The subjects were randomized into 2 different groups (group supplementation or placebo) using simple random sampling.

Inclusion and control criterias were: women with SLE, aged 18-43 years old, duration of disease ≤ 1 year, SLEDAI scores ≥ 5, experienced hypovitaminosis D, and did not taking any medicationcontaining vitamin D (diet containing vitamin D was not counted as vitamin D supplementation). The exclusion criterias were: patients suffered severe infection (sepsis), trauma, liver disease with AST and ALT 2.5 above normal, renal disease with GFR≤ 60 (cockrofgault), oliguria <400 cc / day, pregnancy, and breastfeeding.

This study was approved by the Ethics Committee of the Faculty Medicine of Brawijaya University/Dr. Saiful Anwar Hospital. Informed concent has been obtained from all subjects.

*Recruitment Procedures Samples*

Patients who met the inclusion and exclusion citerias, and agreed to participate were asked to sign the informed consent, had initial examination and physical examination. SLEDAI scores and FSS score were also evaluated. Then the research subjects were supplemented with vitamin D3 softgel/ cholecalciferol 1200 IU/day or 30 mg/ day while the controls were given a placebo.

During the study, patients were routinely followed up in Rheumatology Clinic every Monday or Wednesday to monitor the side effects of Vitamin D supplementation and taking the next month medication. Supervision of drug consumption were done by the patients and their family members who were willing to supervise the patient the early days to count the number of remaining medicine,in order to measure the amount of medicine that had been taken. The monitoring was carried out for 3 months. Monitoring of SLEDAI score, FSS score as well as vitamin D levels was repeated in the end of the study to each sample.

*Statistical Analysis*

The differences of vitamin D levels before and after supplementation of vitamin D were analyzed using paired-sample t-test, p <0.05 was considered significant. In addition,the relationship of disease activity and fatigue conditions were analyzed using Pearson correlation test, and the statistical analysis was performed using SPSS for Windows 17.

**Result**

*Characteristics of Research Subjects*

The number of patients who met the inclusion criteria and exclusion criteria were 20 subjects for treatment groupand 19 people for placebo group. Characteristics of the patients in this study are presented in Table 1.

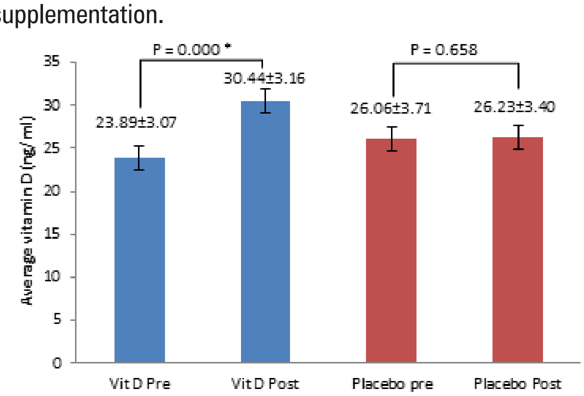
**Table 1.** Characteristics of Subjects

| Characteristic | Supplementation mean±SD | Placebo mean±SD | *P* |
|---|---|---|---|
| Age (year) | 28.25± 6.97 | 27.26±6.76 | 0.55 |
| Duration of illness (month) | 3.55±1.90 | 2.74±1.86 | 0.17 |
| Level of Vitamin D (ng/ml) | 23.89± 3.07 | 26.06±3.71 | 0.86 |
| SLEDAI | 12.65±4.85 | 10.74±2.75 | 0.19 |
| *Fatigue Severity Score (FSS)* | 5.41±1.02 | 4.86±0.77 | 0.12 |
| Level of ds DNA | 226.8±82.1 | 238.3±65.0 | 0.68 |
| Level of Calsium (mg/dl) | 8.85±0.393 | 0.898±0.384 | 0.322 |
| Early Manifestations(%) | | | |
| • Mucocutaneous | 6 (30 %) | 9 (47 %) | |
| • Arthritis | 5 (25 %) | 5 (26 %) | |
| • Nephritis | 8 (40 %) | 4 (21 %) | |
| • Haematology disorder | 7 (35%) | 8 (42%) | |
| • Serositis | 3 (15%) | 2 (11%) | |
| • Cerebral | 1 (5% ) | 0 ( 0 %) | |
| Treatment (%) | | | |
| • non immunosupressant | 2 (10 %) | 3 (15.8 %) | |
| • Azathioprin | 5 (25 %) | 5 (26.3%) | |
| • Cyclophosphamid | 2 (10 %) | 1 (5.30%) | |
| • Methyl Mecofenolat (MMF) | 6 (30 %) | 3 (15.8 %) | |
| • Chloroquin | 5 (25 %) | 7 (36.8 %) | |

*Vitamin D Level*

The difference levelof vitamin D before and after supplementation in control and intervention groups are presented in Figure 1.

**Figure 1** Comparison level of vitamin D pre and post supplementation.

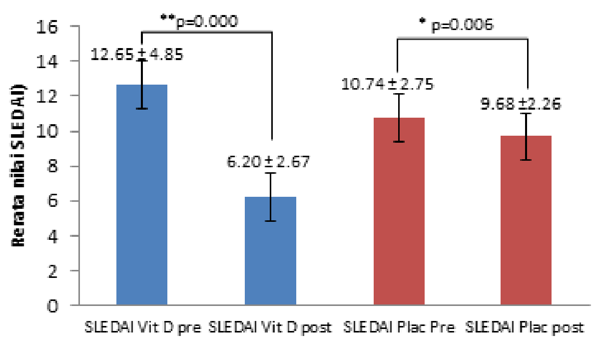



Oral vitamin D supplementation significantly increase the vitamin D level in intervention group, as shown above. There was significant difference of vitamin D level between pre and post vitamin D supplementation in SLEpatients (p=0.000). While in group of patients with placebo, there was no significant difference between pre and post placebo administration (p=0.658).The mean of delta vitamin D level before and after intervention were 6.55 ± 0.09 ng/ml in experimental group and only 0.17±1.63 ng/ml in control group.

*SLEDAI Score*

This study showed that SLEDAI score before and after supplementation had a significant difference, in both group receiving oral vitamin D and oral placebo. The experimental group showed a decrease in the average value of SLEDAI from 12.65±4.85 to 6.20±2.67 with a mean decreased 6.45 ± 2.18. Whereas, the placebo group showed a decrease average value of SLEDAI from 10.74±2.75 to 9.68±2.26 with the mean of decrease 1.06±0.49 .

**Figure 2** Comparison of the decreased SLEDAI score in patients post supplementation versus pre supplementation.



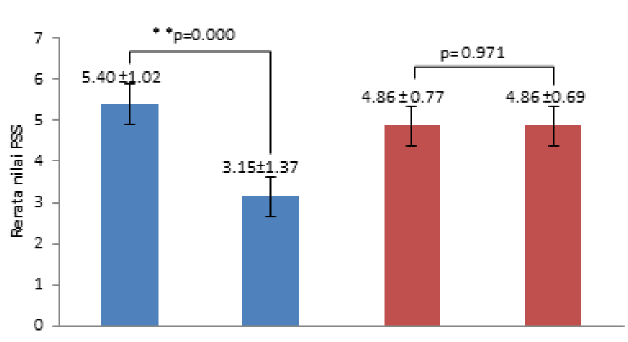

The SLEDAI score in post supplementation was lower than pre supplementation group (p=0.000). Same as supplementation group, SLEDAI score in post placebo tend to be lower than pre placebo group (p= 0.006).

There was a significant decrease of SLEDAI score in both groups after 3 months trial.

*FSS value changes before and after supplementation*

This study showed that FSS score before and after supplementation had a difference, both in the vitamin D supplementation and the placebo group. Vitamin D supplementation group showed a significant decreasing of the average value of FSS score with the mean decrease was 2.25 ± 0.73. It means there was a fatigue improvements in group of SLE patients receiving oral vitamin D supplementation. In the placebo group, the decrease was just slightly, with average decrease value only -0.005 ± 0.62, and no statistical difference (p>0.05) were found. The FSS score before and after oral vitamin D supplementation can be seen in Figure 3.

**Figure 3** Comparison of FSS score pre and post supplementation.




There was a significant difference between the mean FSS score pre and post vitamin D supplementation in SLE patients (p=0.000). While the average FSS score between patients pre and post placebo in SLE patients showed no significant difference (p=0.971).

The significant improvements were seen in all aspect of FSS questions. The higher significant changes (p<0.001) were seenin: fatigue affects motivation (P-1), physical exercise as fatigue precipitator ( P-2), easy experience of fatigue (P-3), patients often have problems with fatigue (P-5), fatigue affects the physical endurance (P-6), and fatigue as one of the main complained (P-8). While the physical activity disorder (P-4), the fatigue affects the duties and responsibilities of the patient (P-7), and the fatigue effect on the environment, family life and social life (P-9) have p value <0.05.Those result shown at Table 2.

**Table 2** The Result of Various Parameters in FSS Score

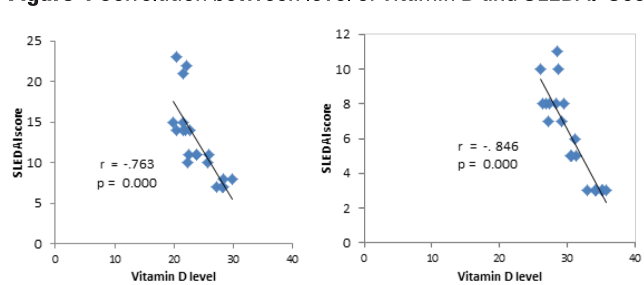
| Item | Pre Supple-mentation Mean ±SD | Post Supple-mentation Mean ±SD | P |
|---|---|---|---|
| Effect on Motivation (P-1) | 5.00 ± 1.12 | 2.95 ± 1.23 | .000 |
| Physical exercise as fatigue precipitator ( P-2) | 4.95 ± 1.19 | 3.20 ± 1.47 | .000 |
| Easy experience of fatigue (P-3) | 5.30 ± 1.26 | 3.20 ± 1.51 | .000 |
| Physical activity disorder (P-4) | 5.45 ± 1.15 | 3.10 ± 1.33 | .011 |
| Patients often have problems with fatigue (P-5) | 5.70 ± 1.26 | 3.15 ± 1.42 | .000 |
| Fatigue affects the physical endurance (P-6) | 5.40 ± 1.43 | 3.25 ± 1.48 | .000 |
| Fatigue affects the duties and responsibilities of the patient (P-7) | 5.70 ± 1.03 | 3.25 ± 1.52 | .001 |
| Fatigue as one of the main complained (P-8) | 5.60 ± 1.05 | 3.25 ± 1.48 | .000 |
| Fatigue effect on the enviroment, family life and social life (P-9) | 5.85 ± 1.27 | 3.15 ± 1.42 | .003 |

Significant if $p < 0.05$

*Correlation of vitamin D level with various parameters*

The correlation of disease activity (SLEDAI) between the supplemented group and the placebo group analyzed by Pearson's correlation test. The aim of correlation test was to determine the relationship between disease activity with vitamin D level before and after treatment.

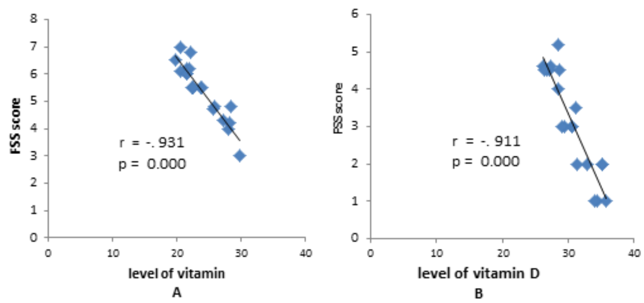
**Figure 4** Correlation between level of vitamin D and SLEDAI Score




A. Before Vitamin D supplementation; B. After Vitamin D suplementation

Correlation test showed an inverse relationship between vitamin D level and disease activity (SLEDAI) before supplementation (p=0.000; r= -0.763). There was a strong relationship between vitamin D level and disease activity (SLEDAI) after supplementation p=-0.846. Negative values indicated an inverse relationship, means when the level of vitamin D escalates there will be a decrease in disease activity (SLEDAI) .

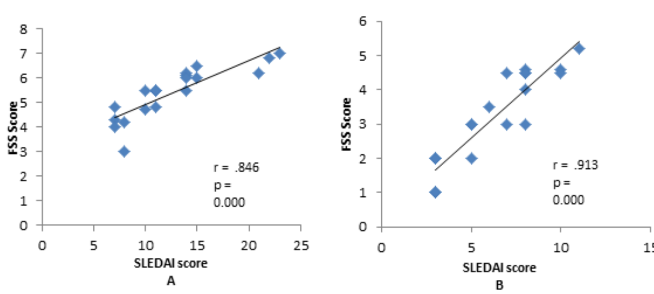
**Figure 5** Correlation between level of vitamin D and FSS score




A. Before Vitamin D supplementation; B. After Vitamin D suplementation

This study showed association between vitamin D level with the Fatigue Severity Scale (FSS), before and after the supplementation. There was an inverse relationship between vitamin D level with FSS before supplementation (p=0.000; r= -0.931), and also vitamin D levels with FSS after supplementation (p=0.000; r=-0.911).

**Figure 6** Correlation between SLEDAI score and FSS Score




A. Before Vitamin D supplementation; B. After Vitamin D supplementation

Correlation analysis showed a strong relationship between disease activity (SLEDAI) and fatigue condition before getting supplementation (p=0.000; r=0.846). There was also strong a relationship between SLEDAI score with FSS after supplementation (p=0.000, r =0.913).

## Discussion

Supplementation of cholecalciferol 1200 IU for 3 months gave a positive effect on the increasing levels of 25(OH)D serum. This showed by significant elevation levels of 25(OH)D in the supplemented group, with average rise 6.55 ± 1.27 ng/ml from the initial baseline. The increasing levels of 25(OH)D serum slightly lower than the previous study, which resulted an increase vitamin D level approximately 10ng/ml with cholecalciferol 1000 IU per day for 3-4 months. Moreover, another study reported an increase level of 25(OH)D to 40ng/ml with 3000IU supplementation of cholecalciferol for three months. [9] However, the change of 25(OH) D level does not always have linear correlation with the supplementation of vitamin D, which mean the same dose supplementation of vitamin D does not always increase the same value of 25(OH) D level in the blood. It is really depend on each individual characteristic.[9] Similar condition also occured in study conducted by Irastorza, where the elevated levels of 25(OH) D ranged from 3.1 ng/ml, with a median dose of 600 IU (dose range of 400-1200 IU per day).[7]

Patients with SLE often develop photosensitivity, malar rash, and discoid rash on his limbs. Therefore, there is a tendency for SLE patients to avoid sunlight and use photoprotection.[10] Some literature stated that in healthy condition, accidental sun exposure in the face and hands is "enough" for fulfilling the vitamin D requirement ranging from 5-10 mg (200-400 IU) of vitamin D. Whereas exposure on 5% skin will produce average 35 nmol/L 25 (OH) D. Contribution of sunlight to produce vitamin D in the SLE patient is relatively low, and would even be lower if they used sunscreen necessarily. A sunscreen with an SPF of 15 will absorb 99% of UVB radiation, and, thus, when sunscreen is applied, it will reduce 99% the synthesis of vitamin D3 in the skin.[11,12] In addition, the presence of renal insufficiency, caused by chronic use of hidrokloroquin and glucocorticoids in SLE patients can also interfere the metabolism of vitamin D.[10]

Target levels of 25(OH)D in SLE patients is 30 ng/ml. In this level, the risk of morbidity caused by hypovitaminosis D will be greatly reduced. In this study, we found that giving 3 month oral vitamin D supplementation would result the 50% of patients achieved the target level with 25 (OH) D value greater than or equal to 30 ng/ml. There is no evidence of additional benefits in 25(OH)D levels more than40 ng/ml.[13]

In this study, there was an inverse relationship between SLEDAI and FSS score with vitamin D level in both groups. However, the result of supplementation group greater than the placebo group with a strong correlation coefficient. The relationship between disease activity with vitamin D levels in SLE patients also demonstrated in a study conducted by Tolaza which showed a negative correlation between the levels of 25(OH)$D_3$ with disease activity score in SLE patients, evaluated usingby ECLAM and SLEDAI. Similar result also found in research conducted by Borba (2009).[14] In Thudi, et al. (2008) study, involve 37 female SLE patients found that 20% of patients who developed clinical manifestation and immunology had lower level of 25(OH)D (<47.7 nmol/L).[15] Patients with low levels of vitamin D will significantly have higher disease activity compared to SLE patients with normal vitamin D level (p <0.003).[15] Similar results were also obtained in study conducted by Petri, et al (2013), who stated that an increased of 20 ng/ml 25 (OH) D level would decreased disease activity in 21% patients with high disease activity score.[13]

Low level of vitamin D is one of the indicator of the ongoing inflammatory process. Inflammation potentially increases the metabolism of vitamin D. This suggests that patients with high SLEDAI scores may get some benefits from vitamin D supplementation. Moreover, supplementing vitamin D can improve immunological abnormalities of patients with SLE, and automatically will improve the clinical manifestations of SLE.[10] The symptoms of vitamin D deficiency is still unclear. But some symptoms may arise as a result of vitamin D deficiency include: fatigue, musculoskeletal disorders (such as muscle pain found in the entire body, muscle stiffness), joint pain, weight gain, high blood pressure, sleep disturbances, impaired concentration , headache, constipation or diarrhea.[17] This study showed before getting any treatment most of subjects experienced severe fatigue conditions with mean FSS score more than 4. After getting 3 months treatment, there was a significant decreased of FSS scores in the supplementation group (compared placebo group) which mean as an improvement of the fatigue condition of the patient.One study reported that nearly 81% of SLE patients experienced fatigue [6], and showed an inverse relationship between level of vitamin D with the degree of fatigue on SLE patient. It is also supported by the results study conducted by Irastorza where the improvement level of vitamin D through supplementation 1,25$(OH)_2D_3$ also improved the condition of fatigue in SLE patients. [7]

In a review article that included 22 studies with a total sample of 3670 patients with musculoskeletal pain and fatigue, stated that 48% of them had a significant vitamin D deficiency, and after improvement of vitamin D levels, subjects experienced some improvement in the degree of pain and muscle weakness, as well as in physical function.[18] Muscle weakness has long been associated with vitamin D deficiency. This happened because there is a vitamin D receptor in skeletal muscle. Hypovitaminosis Dhas been associated with proximal muscle weakness, decreased body stability, and increased risk of falling.[12] Treatment with vitamin D improves muscle function among patients with hypovitaminosis by increasing cross-sectional area of fast-twitch type II A fibers and increase muscle strength of proximal muscle.[19]

Fatigue severity scale (FSS) has been recommended by ACR 2007 at the Ad Hoc Committee on Systemic Lupus Erythematosus response criteria for fatigue to assess the fatigue condition in SLE patients with highvalidity and reliability. FSS has been translated into several languages.[20] The FSS consists of nine questions with a range of values between 1 and 7 on each item question, with score>4 shows a severe condition of fatigue.[20] Nine items from FSS question refers to a variety of conditions that occur in patients who experienced SLE fatigue. These conditions include: physical functioning, vitality, emotional, social, and metal health.[21]

In this study we found that vitamin D supplementation improved the overall FSS conditions, such as the physical functioning, vitality, emotional, social, and mental health, which indicates the presence of significant changes ($p < 0.05$) at 9 item questions in FSS.This condition is consistent with the results from research conducted by Lorentzen (2014) who found SLE patients with fatigue will cause a decrease in physical, social and mental function.[22]

This study also showed there was a significant association between disease activity and fatigue. Previous studies reported that SLE patient with severe fatigue had higher disease score activity. However, the main clinical features of higher disease activity is not the fatique, but the significant decreased of physical distress (headache, anxiety, musculosceletal disorder, stomachache, fever, and weight loss).[23] Therefore, the relationship between fatigue and disease activity SLE is still controversial**.** There are some inconsistent results of the fatigue relation with SLE disease activity in previous studies. Antoni, et al.(2007) metaanalysis study, identified 34 studies published in the last 40 years. From the studies, there were 10 studies that evaluated the correlation between disease activity and fatigue in SLE patients. The 8 studies showed a significant relationship between disease activity with fatigue condition in SLE patients, but the other two did not.[6,24-30] Different results obtained from Wang, et al.(1998 ), which found no relationship between disease activity with fatigue.[31]

In this study, there was no adverse effects found in the supplemented group. According to the European Commission's Scientific Committee on Food (SFC), tolerable upper intake levels (UL) of vitamin D is 50 mcg/day equivalent to 2000 IU of vitamin $D_3$, while the United Kingdom Expert Group on Vitamins and minerals (EVM) set a dose of 25 mg/day. Maximum NOAEL (no observed adverse effect levels) of vitamin D is 250 mcg/day with toxicity effects may include hypercalcemia, hypertension, nausea, vomiting and even could interfere renal function.[32]Other literature mentioned that toxicity will occur if the patient is taking more than10,000 IU of vitamin D per day for months to years. Until now there is no literature available explaining the toxicity of cholecalciferol consumption less than 10,000 IU per day.[9] Toxicity that occurs as a result of the increase in calcium levels are considered as secondary toxicity. This toxicity occurs gradually until levels of 25 (OH) D exceeds 150 ng/ml.[32]

In this research we evaluated the calcium levels both pre- and post-treatment in the supplementation group and the placebo group, at the end calcium results were within normal range.

## Conclusion

The supplementation of vitamin D 1200 IU per day in SLE patients improved disease activity and fatigue conditions.

## Research weakness

The weaknesses of this study are the number of subjects enrolled in this study was the minimal sample required and we did not use a double blind study.

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# Validity And Reliability Of Lupus Quality Of Life Questionnaire In Patients With Systemic Lupus Erythematosus In Indonesia

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**Abstract**

**Background**: The development of Systemic Lupus Erythematosus (SLE) treatment has led the increased of patients survival. Quality of life has became a value based medicine component that should be evaluated in treating SLE. One standardized questionnaire to asses the quality of life in SLE patients is Lupus Quality of Life (Lupus QoL). Currently, in Indonesia, there has not been any spesific questionnaire to asses the quality of life in SLE patients. This study aims to prove that Lupus QoL is valid and reliable to asses the quality of life in SLE patients in Indonesia**.**

**Methods**: This study used cross sectional study method. Firstly, we translated the Lupus QoL into Indonesian language, then we tested to 10 respondents. Then, we continued the study with larger sample size. We analyzed the reliability of the test and the re-test result using the interclass coefficient correlation and the internal consistency of the tests using cronbach alpha. Construct validity was evaluated using multi trait scaling analysis and the extrenal validity was evaluated using correlation between domains in short form 36 (SF 36) with Lupus QoL and with disease activity.

**Results:** Data collection was done to 65 SLE patients between October – November 2015 in RSCM. The test has good external validity SF 36 ($r=0.38$-$0.66$, $p<0.05$) and good construct validity ($r > 0.4$; range: 0.44-0.93). The ICC value in one week $>0.7$ and Cronbach $\alpha$ was $>0.7$ in each domain. The correlation between lupus QoL and the disease activity was weak and consistent with other studies.

**Conclusion**: Lupus QoL questionnaire is valid and reliable to asses the quality of life in SLE patients in Indonesia.

**Key words:** Quality of Life, Systemic Lupus Erythematosus, Lupus QoL, Validity, Reliability

## Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that caused chronic inflammation with varied clinical manifestations and prognosis.[1] SLE is classified by period of acute attack and remission.[2] SLE patients have higher morbidity and mortality compared to general population.[1,2] The development of SLE therapy has benefit in increasing the survival of SLE patients. This shift the fact that quality of life (QoL) in SLE patients is now substantial to be evaluated. However, there is a different goal perception between the clinicians and the patients. International consensus has written that QoL is a basic evaluation in patients with SLE that has to be assessed by clinicians beside the disease activity, organ damage, side effect of therapy and economic impact. [3-9] The QoL of SLE patients is lower than general population or others chronic illnesses. The disease activity and organ damage reated to SLE progression inconsistently impact the QoL in SLE patients.[3,10-14] While, the disease or organ damage prior to SLE has a strong connection to reduce QoL in SLE. [15-16]

SLE QoL can be evaluated by general or spesific questionnaire.[17] The general questionaire that proven valid and reliable are *Short Form 36 Health Survey* ( SF 36 ) and *Euro-QoL 5 - Dimensional* (EQ 5D).[17] However, since its used for general population, these questionaires do not cover spesific SLE impairment, such as sleep disturbances, sexual dysfunction, and body perception disturbances.[18] Nowdays, specific questionaires for assesing QoL in SLE patients, such as Lupus QoL, SLE QoL dan L – QoL. These three questionnaire have been proven valid and reliable to measure quality of life in SLE. Clinical review by Holloway et al has shown that Lupus QoL has a better validity in each evaluated domain compared to others.[17,19-25] Lupus QoL has proven valid and reliable to evaluate the quality of life in SLE. Still there has no research to evaluate the validity and reliability of Lupus Qol in Indonesian language in SLE patients in Indonesia. This research is trying to prove the validity and reliability in Lupus Qol in Indonesian language to evaluate the quality of life in SLE patirnts in Indonesia.

## Methodology

### *Study design*

This was a cross sectional study in the SLE patients that went to the internal medicine clinics in RSCM in October until November 2015.

### *Subject*

Subjects were included using consecutive sampling method. SLE patients who visited RSCM Internal Medicine clinics in period October – November

2015 and willing to enter the study were included as subjects. Subjects were excluded if they have cognitive impairment, so that their quality of life can not be evaluated.

All subjects were evaluated by analyzing their history in medical records, taking comprehensive anamnesis, physical examination, and labortory examination. The collected data, include:

1. Subject characteristic :age, sex, body weight, last education, insurance, duration of SLE, diagnosis, disease activity by using MEX SLEDAI and drugs that were used.
2. Physical examination : arthritis and joint swelling that were evaluated by MEX SLEDAI.
3. Quality of life were evaluated using Lupus QoL and SF 36 questionnaire.
4. Reevaluation of Lupus QoL, one week after first encounter.

*Lupus QoL Questionnaire Preparation*

Lupus QoL quistionnaire were prepared within two phase. First, the original version of Lupus QoL questionnaire was translated to Indonesian language. We have got permission from the original author for the translating process. For translating purpose, we used 2 certified translator from *Lembaga Bahasa Universitas Indonesia* (LBUI). The translation then were evaluated and synthesized into Indonesian Lupus QoL questionnaire. The validity of the Indonesian Lupus QoL quistionnaire version then was tested to 10 subjects, the subjects are allowed to give input for the fixation. If the questionaire validity no difference with the orginal version, then we can continue to the second phase. The questionnaire should be fixed, if it is still not valid. The validity process could be done several times until we got the Indonesian version quiestionaire that have no difference validity with the orginal version.

In the second phase, we assessed all the study subjects using the Indonesian version of Lupus QoL quistionnaire. For external validity, we used SF 36 quistionnaire as our control.

*Data analysis*

All of the data were documented in study form. Data were validated and processed, using SPSS (*Statistical Package for the Social Sciences*) 20$^{th}$ version. Data were analyzed using Kolmogorov – Smirnov test, Pearson or Spearman test, *Intra class Correlation Coefficient* (ICC) and Cronbach α coefficient.

The validity of Lupus QoL questionnaire was evaluated by analysing external and construction validity. The external validity was analyzed by having correlation coefficient between SF 36 and Lupus QoL. The construction validity was analyzed by having the correlation coefficient in each question compared to total number.

The Cronbach α value was considered good when ≥ 0.7, *the* Spearman *correlation coefficient* considered strong when > 0.5.[11] In this study we used cut off value of r ≥0.7 was considered strong, 0.3 – 0.7 was moderate and > 0.3 were weak.[24]

**Results**

*Subject charasteristic*

Sixty five patients SLE patients were enrolled to the study using the consecutive sampling method. The characteristics of the subject were shown in the table 1.

**Table 1.** Subject Epidemiological Characteristic

| Characteristic | Frequency ( % ) |
|---|---|
| 1. Sex | |
| Male | 2 (3.1) |
| Female | 63 ( 96.9) |
| 2. Age | |
| 18 – 25 | 1 (1.5) |
| 26 – 30 | 4 ( 6.2) |
| 31 – 35 | 11 (16.9) |
| 36 – 40 | 35 ( 53.8 ) |
| 41 – 60 | 14 ( 21.54) |
| 3. Education | |
| < Elementary School | 1 (1.5) |
| Elementary School | 4 ( 6.2) |
| Junior High School | 11 (16.9) |
| Senior High School | 35 ( 53.8 ) |
| University ( D1 – S3 ) | 14 ( 21.54) |
| 4. Occupancy | |
| Work | 22 ( 33.8 ) |
| Housewives | 36 ( 55.4 ) |
| Student | 4 ( 6.2 ) |
| Not working | 3( 4.6 ) |
| 5. Marital Status | |
| Married | 46 (71) |
| Not married/ divorce | 19 (29) |
| 6. Duration of illness | |
| < 5 years | 31 ( 47.7 ) |
| 5 – 10 years | 24 ( 36.9) |
| 11 – 15 years | 7 ( 10.8 ) |
| More than 15 years | 3( 4.6 ) |
| 7. Organ Involvement | |
| Mucocutaneus | 61 |
| Musculosceletal | 59 |
| Hematology | 14 |
| KIdney | 10 |
| Neuropsychiatric | 1 |
| 8. Organ involvement combination | |
| Mucocutaneus and musculosceletal | 38 ( 58.5 ) |
| Mucocutaneus and hematology | 2 ( 3.1 ) |
| Mucocutaneus, musculosceletal and kidney | 6 ( 9.2 ) |
| Mucocutaneus, musculosceletal, hematology | 9 ( 13.8 ) |
| Kidney, hematology, neuropsychiatry | 2 ( 3.1 ) |
| Mucocutaneus, kidney, hematology | 2 ( 3.1 ) |
| Mucocutaneus, musculoskeletal, kidney, hematology | 3 ( 4.6 ) |
| Mucocutaneus, musculoskeletal, kidney, neuropsychiatry | 1 ( 1.5 ) |
| 9. Therapy | |
| Steroid | 16 ( 24.6 ) |
| Single Immunosupresant agent | 10 ( 15.4 ) |
| Steroid + Chloroquine | 14 ( 11.5 ) |
| Steroid + Azatioprine | 18 ( 12.3 ) |
| Steroid + Metothrexate | 1 ( 1.5 ) |
| Steroid + Mofetil mycophenolate | 3 ( 4.6 ) |
| Steroid + Cyclosporine | 2 ( 3.1 ) |
| Imuran + Chloroquine | 1 ( 1.5 ) |
| Steroid + Cyclophosphamide | 1 ( 1.5 ) |
| More than 2 regimens | 7 ( 10.8 ) |
| Without treatment | 2 ( 3.1 ) |
| 10. MEX SLEDAI | |
| 0 | 48 ( 73.8 ) |
| 1 | 1 ( 1.5 ) |
| 2 | 8 ( 12.3 ) |
| 3 | 2 ( 3.1 ) |
| 4 | 1 ( 1.5 ) |
| 6 | 4 ( 6.2 ) |
| 9 | 1 ( 1.5 ) |

*Lupus QoL questionnaire translation*

In the validity process, the 10 subjects concluded that indonesian version of Lupus QoL was understandable and did not need any fixation. The subjects took about 5 – 10 minutes to give their answers. Special explanation were given to the 15th and 16th statements in Lupus QoL, the sexual relationship were considered as intimate relationship in the Indonesian version of Lupus QoL. This explanation were discussed and agreed by the original author of Lupus QoL. The Indonesian version of Lupus QoL then translated back to English, and the result was compared to the original version of Lupus QoL questionnaire by 2 native speaker. The difference then evaluated and discussed. In this study, we found no difference between Indonesian and orginal version of Lupus QoL questionnaire.

*SF 36 questionnaire*

In this study, SF 36 questionaire was given to the subject in the first meeting in day 1. In this study the SF 36 was proven to have a good internal consistency with cronbach $\alpha > 0.7$. The number of total cronbach α was 0.749 within range of 0.774 – 0.802 in each domain. The distribution of the data was not normal except in Vitality (VT) and Mental Health (MH) domain.

*Lupus QoL Indonesia*

The results from this study, the data were not distributed normally by Kolgomorov-Smirnov test with $p<0.05$. The mean of total Lupus QoL score was 7.411 with median 75.74 (25.74 – 100). The lowest mean score was in fatigue domain (68.91) and the highest was planning (79.36).

*External Validity*

Four domains that assessed in Lupus QoL and SF 36 were equal. The domains are: physical health and vitality; fatigue and vitality; pain and bodily pain; emotional health and mental health. The correlation test were done to assess any different between the four equal domains. Lupus QoL have moderate with statistically significant correlation with SF 36 (r : 0.655, $p<0.05$). Each domains (physical health, pain, emotional health, and fatique) also showed moderate with statistically significant corellation between Lupus QoL and SF 36, as presented in Table 2.

**Table 2.** Correlation between each domain in Lupus QoL and SF 36

| No | Lupus QoL Domain | SF 36 Domain | r | P |
|---|---|---|---|---|
| 1 | Physical Health | Physical Function | 0.445 | 0.000 |
| 2 | Pain | Bodily Pain | 0.381 | 0.005 |
| 3 | Emotional Health | Mental Health | 0.636 | 0.000 |
| 4 | Fatigue | Vitality | 0.489 | 0.000 |

In this study, we also analyzed the ability of Lupus QoL to differentiate the different quality of life related to disease activity. The correlational analysis showed that the corelation between domain in lupus QoL Indonesia and disease activity was weak and not significant (r : -0.06 - -0.16, p : 0.19 – 0.64), as presented in table 3.

**Table 3.** Correlation between domain in Lupus QoL Indonesia and Disease Activity

| No | Domain | r | p |
|---|---|---|---|
| 1 | Physical health | -0.10 | 0.42 |
| 2 | Pain | -0.10 | 0.42 |
| 3 | Planning | -0.06 | 0.64 |
| 4 | Intimate relationship | -0.16 | 0.19 |
| 5 | Burden to others | -0.10 | 0.43 |
| 6 | Emotional health | -0.13 | 0.32 |
| 7 | Body image | -0.13 | 0.31 |
| 8 | Fatigue | -0.11 | 0.37 |
| 9 | Total Lupus QoL | -0.13 | 0.31 |

This study was also showed that there was no difference between active SLE compared to inactive SLE, as seen in Table 4.

**Table 4.** Mean difference of total Lupus QoL Indonesia according to disease activity

| Domain | MEX SLEDAI<2 (n=49) | MEX SLEDAI ≥2 (n=16) | Beda rerata | P |
|---|---|---|---|---|
| Physical health | 79.34 | 75.00 | 4.34 | 0.38 |
| Pain | 76.02 | 72.40 | 3.62 | 0.72 |
| Planning | 82.14 | 70.83 | 11.31 | 0.27 |
| Intimate relationship | 78.06 | 77.34 | 0.72 | 0.97 |
| Burden to others | 70.68 | 71.35 | -0.67 | 0.34 |
| Emotional Health | 70.32 | 64.58 | 5.74 | 0.37 |
| Body Image | 77.86 | 69.38 | 8.48 | 0.34 |
| Fatique | 68.88 | 64.06 | 4.82 | 0.48 |
| Total Domain | 75.36 | 70.27 | 5.09 | 0.47 |

*Construction Validity*

**Table 5.** Correlation between domain and total score of Lupus QoL Indonesia

| DOMAIN | PH | P | PL | IR | BO | EH | BI | F |
|---|---|---|---|---|---|---|---|---|
| Total | 0.81 | 0.85 | 0.72 | 0.46 | 0.56 | 0.84 | 0.67 | 0.76 |

PH : *Physical health*, P: *Pain,* PL: *Planning,* IR: *Intimate relationship*, BO: *Burden to others,* EH: *Emotional Health,* BI: *Body Image,* F: *Fatigue*

In this study, the correlation in the domain of intimate relationship, burden to others, body perception has value between 0.3 to 0.7 and in domain of physical health, planning, emotional health and fatigue showed higher value, above 0.7.( 0.72 – 0.85 ). Spearman test showed that every question have r >0.4. (0.44 – 0.9, CI: 95% dan $p<0.05$) to the total domain score.

*Reliability*

Lupus QoL questionnaire reliability by analyzing the Intra class Correlation Coefficient (ICC) in test and re test. Internal consistency was evaluated by measuring the *cronbach α*.

**Table 6.** Cronbach α score in Lupus QoL Indonesia

| Lupus QoL | Cronbach α |
|---|---|
| Total | 0.850 |
| *Physical health* | 0.867 |
| *Pain* | 0.855 |
| *Planning* | 0.868 |
| *Intimate relationship* | 0.892 |
| *Burden to others* | 0.887 |
| *Emotional Health* | 0.858 |
| *Body Image* | 0.882 |
| *Fatigue* | 0.867 |

In this study Lupus QoL Indonesia showed a good internal consistency, with value of cronbach α >0.7

**Table 7.** Intraclass correlation coefficient in Lupus QoL Indonesia

| Test and Re Test | *Intraclass correlation coefficient* |
|---|---|
| Total | 0.948 |
| Physical health/ PH | 0.892 |
| Pain/ P | 0.802 |
| Planning/ PL | 0.748 |
| Intimate relationship/ IR | 0.738 |
| Burden to others/ BO | 0.839 |
| Emotional Health/ EH | 0.944 |
| Body Image/ BI | 0.949 |
| Fatigue/ F | 0.913 |

The test and re test reliability of Lupus QoL Indonesia was good with ICC > 0.7.

## DISCUSSION

This cross sectional study with 65 patients. Female was the frequent sex with 63 patients (97%). This pattern was consistent with studies in England 152 patients (95%), United States of America 174 patients (94%), China 182 patients (88.9%), France 160 patients (88%), Italy 104 patients (88.9%) and Turkey 128 patients (97%).[24-30] The mean of age was 34.97 years (SB 8.551). Median age was 35 years with the oldest was 55 years and the youngest was 19 years. Other studies showed similar characteristic, such as study in Italy, Turkey, China, France, and Iran showed mean age 40.6 years, 37.9 years, 33.9 years, 39.6 years, and 36.8 years, respectively. The level of education in this study was high school in 35 patients ( 53.8% ). This result had the same level in Iran with 11.2 years (SB 3.8).[28] The disease duration of this study was 5.98 years (SB 4.616) with p< 0.05. Similar study showed that the disease duration was more than 5 years, in Italy 10.63 years ( SB 7.84 )[21], Turkey 5.97 years (SB 4.99)[22], Iran 8.2 years (SB 3.8).[23] Mucocutaneus involvement was the frequent organ involvement in this study, 61 patients (93.84%). The combination of mucocutaneus and musculosceletal was the frequen combination in this study 38 patients (58.5%). Combination therapy by steroid and azatioprin was the frequent combination with 18 patients (12.3%).

Fourty eight patients (73.8%) had an inactive SLE with 0 in MEX SLEDAI. The highest disease activity was 9 with MEX SLEDAI tertinggi adalah 9 in 1 patients (1.5 %). This study showed that most of all SLE patients was in inactive state of SLE. This results similar with other studies results in Italiy 102 patients (87%), Turkey 75 patients (56.8%), Iran 71 patients (78.5%) and France 105 patients (62%).

*SF 36 questionnaire*

In this study we use the SF 36 questionnaire, the results showed good internal consistency with *cronbach* α was 0.799. The total cronbach alpha was 0.749. Other studies showed that SF 36 Singapore had cronbach α 0.84 – 0.94.[18] and China 0.72 – 0.91.[18]

*Lupus QoL Indonesia questionnaire*

The normality study showed that the distibution was not normal with p<0.05. The spearman correlation study was used to evaluate the correlation. The mean of Lupus QoL total score was 74.11(SB 15.04) with Planning domain had a highest score with total mean 79.36 (SB 20.28) and the lowest domain was fatigue with mean value 67.69 (SB 20.03). The rank of total domain score from the lowest was fatigue, emotional health, burden to others, pain, body image, intimate relationship, physical health, planning. This study was also showed that there was a decrease in quality of life in each domain in SLE patients. This result was consistent with previous studies.

*Validity*

The validity of Indonesian Lupus QoL was done by evaluating the external validity and construction validity.

External validity

In this study the correlation between equal domains in SF 36 and Indonesian version of Lupus QoL was moderate and significant with r : 0.655 and p<0.05 ). Each domain has moderate corellation ( r :0.404 – 0.636 ). Similar studies showed similar results England (r : 0.71)[24], United States of America (r: 0.48 – 0.573) [25], France (r: 0.59 – 0.78) [30], Iran (0.4) [28], Turkey (0.66 – 0.74).[27]

We also analyzed the ability of Lupus QoL Indonesia to differentiate the quality of life in two different condition, active and inactive SLE. By using the MEX SLEDAI to determine the status of the disease activity. However, we found that the corelation were weak and not statistically significant ( r : -0.06 - -0.16, p : 0.19 – 0.64 ). The intimate relationship domain had the highest corellation with disease activity and the planning domain was the lowest. Using the Mann Whitney test, we found that there were no differences in results between the active and inactive group.The result was similar to previous studies that showed the correlation between quality of life and disease activity was inconsistent.[12,15,17] In China, there was a decrease in quality of Life in each domain, except body image domain.[29] In Iran, a decrease showed in all domain of Lupus QoL, but only in planning, emotional health and body image that had a statistically significant.[28] In France, only in physical health, pain and intimate relationship domain were decrease.[30] In Turkey, a statistically significant decrease showed in all of Lupus QoL domain.[27] In USA, a decrease also showed across all of Lupus QoL domain, but statistically significant only found in physical health, planning, burden to others and emotional health.[25]

These differences happened not only because of the different characteristic of SLE patients and the different instrument used to evaluate disease activity, but also because of the limitation of the cross sectional study method which can not assessed other external factors that could influence the QoL, beside the SLE condition itself. In this study, we proved that Lupus QoL Indonesia is externally valid.

Construction Validity

The construction validity in Lupus QoL Indonesia was proven by evaluating the correlation in each total domain score to the total Indonesian Lupus QoL score and correlation between each questions and the total domain score of Indonesian Lupus QoL. We proved that Lupus QoL Indonesia had a good construction validity if the correlation coefficient were > 0.4 in *multi trait scaling*. The study results showed that physical health, planning, mental health and fatigue were correlated strongly with total score of Indonesian Lupus QoL and others were moderately correlated. All of the results showeed that r > 0.4 with p<0.05. In this study, Lupus QoL Indonesia had a good construction validity.

*Reliability*

Internal Consistency

The study showed that the total cronbach α of Lupus QoL was 0.850 with the highest score in intimate relationship domain and the lowest was in pain domain. The overall value of *cronbach α* was good because its had value > 0.7 (0.86 – 0.89). This showed that Indonesian Lupus QoL has a good internal consistency.

Test and Re Test Reliability

The TRT reliability was evaluated by using the *intra class correlation coefficient (ICC). The result showed that the ICC were* 0.74 – 0.95. Other previous studies showed similar results in England (0.72 – 0.93)[24], Italy (0.9 – 0.98)[26], Turkey (0.88 – 0.94)[27] , China (0.84 – 0.97)[29] and France (0.79 – 0.95).[30] This study proved that TRT reliability of Lupus QoL Indonesia was good.

*Limitation of the study*

We realize that our study has some limitations. Since we used consecutive sampling methods, not all SLE population that come to our centers have the same opportunities to participate in this study. Though, the consecutive sampling methods was the best sampling methods for *non probability sampling*. With the amount of the subject study was appropriate to calculate the possibility of moderate and significant relationship with SF 36. This study only used SLE in ambulatory care setting. The external factors that might had impact on quality of life were not evaluated such as age, level of education, and other disease comorbidities. We also did not exclude or analysis any side effect of the therapy.

## Conclusion

Lupus QoL questionnaire in Indonesian language is valid and reliable to evaluate the quality of life SLE patients in Indonesia. Further, a study with more varied population of SLE patients is needed. Besides, we also need to perform a study to prove the ability of the lupus QoL quistionnaire to detect any change in quality of life of SLE patients that related to their disease activity so that it could be applied in clinical practice.

## Attachment 1

**Kuesioner Lupus QoL**

Kuesioner berikut dirancang untuk mengetahui bagaimana SLE mempengaruhi hidup anda.

Bacalah setiap pernyataan dan berikan tanda centang pada kotak yang paling sesuai dengan apa yang anda rasakan. Jawablah semua pertanyaan dengan sejujurnya.

**Seberapa seringnya dalam 4 minggu terakhir ini**

1. Saya memerlukan bantuan untuk melakukan pekerjaan fisik yang berat seperti menggali di taman, mengecat dan atau mendekorasi, memindahkan perabotan karena penyakit lupus yang saya derita.

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

2. Saya memerlukan bantuan untuk melakukan aktivitas fisik sedang seperti menyedot debu, menyetrika, berbelanja dan membersihkan kamar mandi karena lupus yang saya derita

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

3. Saya memerlukan bantuan untuk melakukan pekerjaan fisik yang ringan seperti memasak, menyiapkan makanan, membuka toples, membersihkan debu, menyisir rambut saya atau membersihkan diri karena lupus yang saya derita.

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

4. Saya tidak mampu melakukan pekerjaan harian seperti bekerja, mengurus anak, mengurus rumah sebaik mungkin karn lupus yang saya derita

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

5. Saya mengalami kesulitan untuk menaiki tangga karena lupus yang saya derita

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

6. Saya kehilangan sebagian kemandirian saya dan menjadi bergantung kepada orang lain karena lupus yang saya derita

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

7. Saya harus melakukan hal – hal dengan kecepatan yang lebih lambat karena lupus yang saya derita karena lupus yang saya derita

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

8. Saya mengalami gangguan pola tidur karena lupus yang saya derita.

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

9. Saya tidak dapat melakukan kegiatan sesuai keinginan saya karena rasa sakit yang disebabkan lupus

   ☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

10. Rasa sakit yang saya derita karena penyakit lupus mempengaruhi kualitas tidur saya.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

11. Rasa sakit akibat lupus yang saya derita begitu parah sehingga membatasi mobilitas saya.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

12. Saya tidak berencana menghadiri berbagai kegiatan di masa yang akan datang karena penyakit lupus.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

13. Saya tidak dapat mengatur hidup saya dengan baik karena ketidakpastian lupus yang saya derita.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

14. Kondisi lupus yang saya derita bervariasi dari hari ke hari sehingga membuat saya sulit untuk berkomitmen dengan acara – acara sosial saya

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

15. Saya kurang tertarik pada hubungan seksual karena sakit yang saya rasakan akibat lupus.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

16. Saya tidak tertarik pada hubungan seks karena penyakit lupus saya.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

17. Saya khawatir penyakit lupus yang saya derita menyebabkan stress bagi mereka yang dekat dengan saya

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

18. Saya merasa prihatin jika saya menyebabkan kekhawatiran bagi mereka yang dekat dengan saya karena penyakit lupus yang saya derita

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

19. Saya merasa menjadi beban bagi keluarga dan atau teman saya karena lupus yang saya derita

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

**Dalam 4 minggu terakhir saya merasa lupus membuat saya**

20. Marah

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

21. Sangat muak dengan keadaan saya sehingga tidak ada yang bisa menyenangkan saya

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

22. Sedih

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

23. Cemas

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

24. Khawatir

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

25. Kurang percaya diri

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

**Seberapa sering dalam 4 minggu terakhir**

26. Penampilan fisik saya akibat lupus mengganggu saya menikmati kehidupan.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

27. Saya merasa penampilan saya karena lupus (dengan rash, kenaikan berat badan/ penurunan berat badan) membuat saya menghindari pertemuan sosial

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

28. Ruam kemerahan pada kulit yang disebabkan oleh lupus membuat saya merasa kurang menarik

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

29. Rambut rontok yang disebabkan oleh lupus membuat saya merasa kurang menarik

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

30. Kenaikan berat badan yang saya alami akibat pengobatan lupus membuat saya merasa kurang menarik.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

31. Saya tidak dapat berkonsentrasi untuk waktu yang lama karena lupus yang saya derita.

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

32. Saya merasa lelah dan lesu karena lupus yang saya derita

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

33. Saya harus tidur lebih awal karena lupus yang saya derita,

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

34. Saya merasa kelelahan pada pagi hari akibat lupus yang saya derita

☐ Setiap saat ☐ seringkali ☐ cukup banyak ☐ Kadang-kadang ☐ Tidak pernah

**Pastikan anda telah menjawab setiap pertanyaan.**

Keterangan tambahan : Hubungan seksual dan hubungan seks pada pernyataan 15 dan 16 diartikan sebagai hubungan intim

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# A Successful Management of 29 year old Female with Left Central Retinal Artery Occlusion due to Manifestation of Primary Antiphospholipid Syndrome

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**ABSTRACT**

Ocular involvement in Anti Phospolipid Syndrome (APS) includes a broad spectrum of manifestations from the anterior and posterior segment or the presence of neuro-ophthalmologic features. A female, 29 years old, came to ER handled by ophthalmology department, with chief complaint left visual loss suddenly since 4 hours before admission. Investigations revealed stable vital signs, VOD 20/20, VOS 1/300, funduscopy showed pale and cherry red spot on left retina, OCT revealed hyperreflective of left inner retinal layer, IgG aCL 51.7 U/mL (50.8 U/mL in OPD 3 months later), and the other examinations were within normal limit. Patient was diagnosed with Central Retinal Artery Occlusion due to Primary Antiphospolipid syndrome. She was performed occular massage and anterior chamber paracintesis procedure, and given O2 6-8 lpm NRBM, Timolol 0.5% eye drop left eye bid, acetazolamide 250 mg bid, *Kalium Slow Release* 1 tab qd, Levofloxacine eye drop 1 drop/hour post surgery. After the result of IgM aCL available, we added warfarin 2 mg qd and aspirin 320 mg qd. Patient was discharged 2 days later as visual acuity improved with VOD 20/20 and VOS 0.5/60.

**Key words:**

Central retina artery occlusion, primary anti phospolipid syndrome, anti cardiolipin antibody

## Introduction

Ocular involvement in APS includes a broad spectrum of manifestations from the anterior and posterior segment or the presence of neuro-ophthalmologic features.[1-4] In brief, conjuctival telangiectasia or conjuctival microaneurysms, episcleritis, limbal or filamentary keratitis and iritis have been described as the APS ocular features from the anterior segment,[5-9] vitritis, retinal detachment, posterior scleritis, branch or central retinal vein occlusion, bilateral choroidal infarction, cilioretinal artery occlusion, venous tortuosity, retinal hemorrhages, cotton-wool spots and central serous type chorioretinopathy from the posterior segment[4,8] and monocular or bilateral transient visual loss, transient visual field loss, ischemic optic neuropathy and progressive optic nerve atrophy as the neuroophthalmologic features of APS. It is estimated that the incidence opf APS is approximately 5 cases per 100.000 persons per year, and 88% of primary APS involved ocular involvements.[4,5]

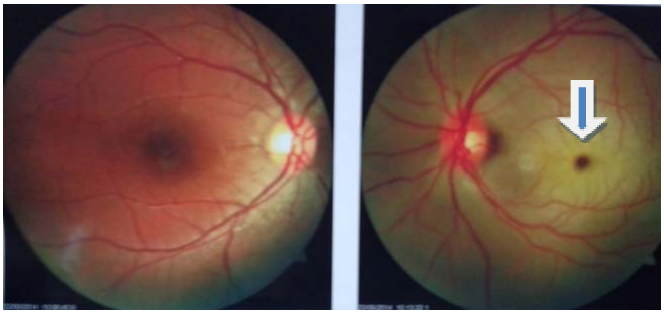
However, case report of the ocular manifestations as the prevailing sign of APS in patients suffering from "unexplained" ocular disease are seldom. Herein, we report a sudden left eye visual loss in a young female without any other risk factors of thrombosis as first manifestation of APS in Malang, Indonesia.

### Case Illustration

A female, 29 years old, came to ER handled by ophthalmology department, with chief complaint left visual loss suddenly since 4 hours before admission when she was playing with her nephews on the bed. Her left eye suddenly could not see anything after she got up from lying on bed. It was painless, persistent, non progressive, and redless. There were no history of joint pain, skin rash, hair loss, fever, eye disease, and episodes of thrombosis before. There weren't also history of trauma, hypertension, diabetes, dyslipidemia, malignancy, heart disease, blood disorders, nor other systemic diseases. However, both parents passed away due to heart disease and stroke as complications of DM and hypertension. She is an accountant, not yet married, and had regular period. She had never consumed routine medications and had no drug allergy.

Physical examination revealed blood pressure 110/70 mmHg, pulse rate 84 bpm, respiratory rate 12 tpm, axillary temperature 36.7 C, body weight 56 kg, body height 158 cm, and BMI 22.4 kg/m$^2$, VOD 20/20, VOS 1/300, intra occular pressure OD was 19.6 mmHg whether OS was 23 mmHg. Funduscopy showed pale and cherry red spot on left retina. Optical Coherence Tomography (OCT) of the left eye revealed hyperreflective of inner retinal layer that was a sign of intraretinal oedema and ischemia. Anterior segment and the other examinations were within normal limit.

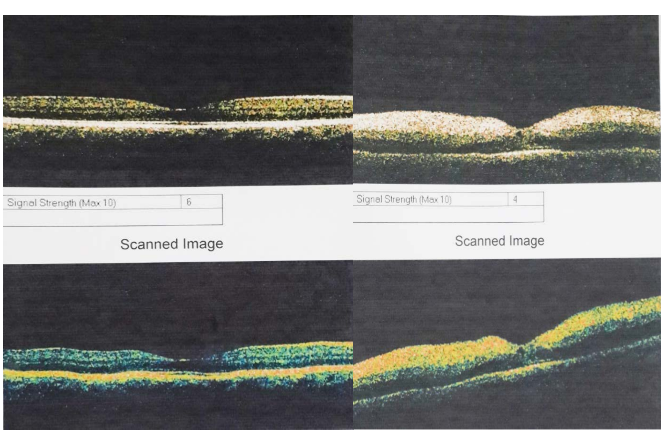
**Figure 1.** Retina Photo of the Patients Showing CRAO (Cherry Red Spot and Pale of the Retina)



Laboratory result showed hemoglobin level 13.60 g/dl, leukocyte count 7.240/µL, hematocrite 40.60 %, thrombocyte count 281.000/µL, (diff count 0.4/0.3/68.6/27.2/3.5). PPT was 11.10 second, aPTT was 29.80 (within normal limit), INR 0.96, random blood glucose 83 mg/dL, Ureum 17.70 mg/dL, Creatinine 0.60 mg/dL, CRP 0.10 mg/dL, ESR 19 mm/hour, fasting blood glucose 72 mg/dL, 2 hours post prandial glucose 92 mg/dL, Hba1c 4.60% (average blood glucose 85.3 mg/dL), total cholesterol 175 mg/dL, triglyceride 56 mg/dL, HDLc 41 mg/dL, and LDLc 92 mg/dL, antidsDNA 66.2 IU/mL (N < 92.6), and ANA test (ELISA) 0.1 (N < 1) units. ECG showed sinus rhytm heart rate 80x/m.

Patient was consulted to internal medicine department to investigate possible cause of blood vessel occlusion in this patient. We suggest to checked for aCL for screening of APS. The result showed IgG anti cardiolipin antibody 51.7 U/mL. We checked again 3 months later in Outpatient Department showed 50.8 U/mL.

**Figure 2.** OCT of Left Eye (Right Picture) that Revealed Hyperreflective of Inner Retinal Layer, Compared to Right Eye (Left Picture) that Was Within Normal Limit




Patient was diagnosed as Central Retinal Artery Occlusion due to Primary Antiphospolipid syndrome. She was performed occular massage and anterior chamber parasintesis procedure, and given O2 6-8 lpm NRBM, Timolol 0.5% eye drop bid on the left eye, acetazolamide 250 mg bid, *Kalium Slow Release* 600mg qd, and Levofloxacine eye drop 1 drop/hour post surgery. After the result of IgG aCL available, we added warfarin 2 mg qd and aspirin 320 mg qd. Patient was discharged 2 days later with improvement of visual acuity (VOD 20/20 and VOS 0.5/60), and aspirin was stopped afterward in OPD with uptitrating warfarin as INR target reached 3.0.

## Discussion

Antiphospolipid syndrome is a hypercoagulable disorder manifested by recurrent arterial and venous thromboses and adverse outcomes in pregnancy that is associated with antiphospolipid (aPL) antibodies.[6] The pathophysiology of retinal artery occlusion in APS is poorly understood, although aPL is implicated in this disorder. aPL affects coagulation and thrombosis in different ways: (1) these antibodies may bind to platelets, upregulating production of thromboxane A2 and expression of glycoprotein 2b-3a, to endothelial cells and monocytes which increase production of tissue factors; or to endothelial cells resulting in an increase in adhesion molecules; which all of them interacts causing thrombosis, (2) the binding of aPL also activates complement, which can initiate an inflammatory cascade resulting in thrombosis. Complement activation has also been linked to fetal loss in APS, (3) another journals also mentioned that coagulation may result from disruption of proteins that regulate thrombosis, such as protein C, by aPL, also antibodies against β-2 glycoprotein I (β-2gpI), a naturally occuring anticoagulant, may induce a prothrombotic state, (4) cardiovascular risk factors such as smoking and estrogen use can help promote thrombosis in APS.[7]

This case demonstrated that the ocular features as the first presenting sign of APS though rare, should alert the clinicians for APS possibility, particularly when conventional risk factors have been excluded and the onset of ocular symptoms are insidious.[5,7,9,11-16] Although the involvement of anterior segment is not rare, the manifestations from the posterior segment such as vasculitis, vitritis, retinal detachment, posterior scleritis and central retinal artery occlusion appear to be more prominent among APS patients.[4,8] Of these, the most common and the most serious is vasculitis, which can result in vasoocclusive disseminated retinopathy. In our case, the patient came with central retinal artery occlusion without any involvement of anterior segment and neuroophthalmology.

Acutely, obstruction of the central retinal artery results in inner layer edema and pyknosis of the ganglion cell nuclei. Ischemic necrosis results, and the retina becomes opacified and yellow-white in appearance. The opacity is most dense in the posterior pole as a result of the increased thickness of the nerve fiber layer and ganglion cells in this region. Furthermore, the foveola assumes a cherry-red spot because of a combination of 2 factors: (1) the intact retinal pigment epithelium and choroid underlying the fovea, and (2) the foveolar retina is nourished by the choriocapillaris. The late stage shows a homogenous scar replacing the inner layer of the retina.[4,6]

The updated International Consensus Statement on classification criteria for definite APS states that the diagnosis of APS should be considered when at least one Clinical Criteria ( (1) Vascular thrombosis, or (2) Pregnancy morbidity; (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week, (b) one or more pre-term births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or recognized features of placental insufficiency, (c) three or more consecutive spontaneous miscarriage before the 10th week of gestation with maternal anatomic, hormonal abnormalities, and chromosomal causes excluded) and one Laboratory Criteria ( (1) Lupus anticoagulant (LA), (2) Anticardiolipin (aCL) antibody of IgG and/or IgM isotype, or (3) Anti-β2-glycoprotein I antibody of IgG and/or IgM isotype, all of those three present in plasma or serum on two or more occasions at least 12 weeks apart).[7,10] Patient in our case presented with arterial thrombosis at central retinal artery and elevated titer IgM aCL on 2 separated examinations, thus already fulfilled diagnostic criteria.

Prevention of thrombosis is a major goal of therapy in patients with aPL antibodies. Therapy is divided into 2 clinical settings: primary prophylaxis (aPL carriers without previous thrombosis) and secondary prophylaxis (patient with APS who have already had a thrombotic events).[7-8]

For patients with documented thrombotic events, long term intensive anticoagulation is recommended on the basis for the type of thrombotic events. Venous events can be treated with unfractionated IV heparin followed by warfarin with a goal INR of 2.5 (range 2-3). Recurrent venous thrombosis has been reported from 3%-24% per year and if it happened, high intensity anticoagulant is recommended (INR range 3-4), or warfarin (INR 2-3) plus aspirin, or switching to LMWH if unstable INR. Evidence to treat arterial event is still lack of evidence. Current therapy includes aspirin only (325 mg/day) and / or warfarin therapy at moderate / high dose. [7,9]

The mainstay of therapy for CRAO is procedure and pharmacologic therapy. Occular massage can dislodge the embolus to a point further down the arterial circulation and improve retinal perfusion. Anterior chamber parasentesis can be performed as a decrease in intraocular pressure is believed to allow greater perfusion, pushing emboli further down the vascular tree. Intra-arterial fibrinolysis is controversial. Limited evidence of improved visual acuity with urokinase is available. A few cases of intra-arterial tissue plasminogen activator (tPA) administration have been observed to be successful.[18]

Immediate medical care to lower IOP includes acetazolamide 500 mg IV/PO once daily and other topical medications. Carbogen therapy (5% CO2, 95% O2) may dilates retinal arterioles and increase oxygen delivery to ischaemic tissue. Hyperbaric oxygen therapy may beneficial if begun within 2-12 hours of onset [18]

Our patient was treated by both rheumatology and ophthalmology department. We gave high dose aspirin and warfarin with target INR 3.0 at the beginning as secondary prophylaxis to prevent another episodes of thrombosis and worsening of arterial occlusion. Ophthalmology department underwent prompt oxygen administration, occular massage, anterior chamber parasentesis, and pharmacological treatment to lower intra occular pressure (acetazolamide, timolol) for giving greater perfusion in the left eye as visual acuity improved. Other therapy modality were not available or still debatable about the benefit.

APS prognosis clearly depends on the severity of the disease, the thrombotic events, recurrences and the side effects of treatment.[3] However, the prognosis of ocular diseases due to APS is not well documented, as long-lasting prospective studies are missing. Though there is still no definite agreement for the duration of anticoagulant treatment, it seems rational and prudent to treat these patients lifelong targeting an INR between > 3.0, while the role, if any, of corticosteroids is unclear. [7,9,17]

## Conclusion

Antiphospolipid syndrome must be suspected in every patient with retinal artery occlusion without any other risk factors. Early diagnosis and prompt treatment are very important to improve visual acuity and prognosis. Collaboration between ophthalmology and rheumatology divisions is needed to support proper management for such particular patients.

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