Correlation Of Clinical Disease Activity Index And Disease Activity Score-28 in Indonesian Rheumatoid Arthritis Patients

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Abstract

Background:Clinical Disease Activity Index (CDAI) stands out amongst other methods in measuring disease activity of rheumatoid arthritis (RA) patient. CDAI is considered to be more practical and cost-effective in daily practice because it requires no laboratory examination. Previous studies conducted overseas revealed that CDAI has good correlation compared to other scoring index in measuring RA disease activity. However, those studies only included pure RA patients without any comorbidity diseases. Indonesian RA patients have distinct clinical profile, in terms of comorbidity conditions, and genetic predisposition which affect the fenotype of the disease.

Objectives: Analyze correlation between CDAI compared to Disease Activity Score 28 CRP (DAS28-CRP) in measuring RA disease activity of RA patients in Indonesia.

Methods: We conducted a cross sectional study to RA patients who visited rheumatology clinic at Cipto Mangunkusumo general hospital from April to May 2016. Data collected included history of illness, physical examination, and recent laboratory results. All data were documented in reseach's form. Both CDAI and DAS28-CRP were measured in each patient by two observers. Correlation analysis between two numeric datas from CDAI and DAS28-CRP were measured with Spearman's Rho. Overall performance was analyzed as additional results using R^2 index.

Result: A total of 119 subjects were included in this study. All subjects were RA patients with comorbidities and were representing quite numbers of Indonesian races characteristic profile. Spearman's Rho = 0,918 and R^2 index =0,831 (83,1%).

Conclusion: There is positive correlation result between outcome of CDAI and outcome of DAS28-CRP in assesing disease activity of Indonesian RA patients.

Key Word: rheumatoid arthritis, Indonesia, correlation, Clinical Disease Activity Index.

Backgrounds

Rheumatoid arthitis is a chronic debilitating disease. A periodic assessment of disease activity is strongly suggested so that disease progression, deformites, and other extraarticular manifestations can be prevented. American College of Rheumatology (ACR) recommendation urges all clinicians to use 'treat-to-target' strategy in treating Rheumatoid Arthritis (RA). It means that the treatments given must targetting remission or low disease activity.[1] This goal can only be achieved if clinicans evaluate patients' disease activity periodically, so they can adjust the dosage or giving combination disease modifying antirheumatic drugs (DMARD).

Clinical disease activity index (CDAI), as one of many disease activity measures endorsed by ACR, has superiority among others in terms of its practical and efficiency aspect. CDAI combine both physician's and patient's assesement while omit requirement of laboratory test (c-reactive protein/CRP), it is beneficial from the physicians standpoint who provide care for RA patients in limited laboratory resources or in limited healthcare budget setting. Another advantage of using CDAI is that its time-efficiency. CDAI can be calculated onsite and does not need to wait laboratory test to come out.

However, previous studies revealed that CDAI outcome has good correlation compared to other measures that incorporate acute phase reactant component.[2-11] Yet those studies cannot be instantly applied to Indonesian patients who might have some comorbidities. Indonesian RA patients have distinct clinical charateristics, includes: (1) Most Indonesian RA patients come with one or more comorbidities, mainly infectious disease; (2) Indonesian RA patients has distinct genetic predisposition compared to caucassian RA patients; this causes a different clinical manifestation and degree of disease progression in Indonesian RA patients. [12-19]

Until today, there has not been any studies that analyze how is the correlation of CDAI outcome compared to other scoring indexes in Indonesian RA patients. This study aimed to answer the question.

METHODS

This is a cross-sectional study which was conducted to RA patients who visited rheumatology clinic at Cipto Mangunkusumo National Referral Hospital on April to May 2016.

Sampling were obtained in consecutive manner. Inclusion criteria for this study were patients who have been well-established diagnosis as RA according to 2010 ACR/EULAR Criteria and agreed to be involved in this study. All subjects were comprehensively examined, with history taking, physical examination, and laboroatory test documentation. CDAI and DAS28-CRP were measured to all subjects. CDAI was used as the main test, while DAS28-CRP was used as the comparator. Each measurements were conducted in blind way by two trained-physicians, the researcher and a rheumatology consultant.

Datas were served as numerics, and analyzed using SPSS 23.0. Interclass coefficient correlation (ICC) were analyzed using Cronbach's alpha. Correlation analysis was measured by Spearman's Rho with its range varies from -1 and +1. A positive correlation coefficient indicates a positive relation between two variables (CDAI and DAS28-CRP). A negative coefficient indicates negative relationship. A zero coefficient indicates no relationship between two variables. Overall performance was measured as additional results using R^2 index, which depicts predictor aspect of one variable outcome to another. R^2>64% suggests a very good prediction model.[20-25]

Results

This study recruited 119 subjects. All subjects were RA patients with at least two comorbidities. The four most frequent comorbidities found were dylipidemia 46.2%, obesity 37%, hypertension 36.1% and infection 26.1%. Eighty-three (69.7%) commorbidities were classified as "other comorbidities" due to the small number of various comorbidities. Those comorbidities were osteoarthritis, cervical-lumbal spondyloarthrosis, rotator-cuff tendinitis, plantar fasciitis, hernia nucleus pulposus, avascular necrosis of hip, carpal tunnel syndrome, asthma, chronic pulmonary obstructive disease, inflammatory bowel disease, gastritis, esophagitis, melena, hematoschezia, dyspepsia, ureterolithiasis, cataract, congestive heart disease, stabil angina, chronic vein insuficiency, dan pregnancy

All subjects represent all range of disease activity from remission to high disease activity. Most subjects fit into range of moderate disease activity, 42% in CDAI and 34.5% in DAS28-CRP. 68.1% subjects were using single DMARD and 1.7% subjects were using biologic agents (Tocilizumab).

Clinical and demographic characteristics of subjects were depicted in **Table 1,** Subject disease activity characteristics were depicted in **Table 2.**

Table 1. Clinical and Demographic Characteristics of Subjects

Characteristics	Result (N=119)
Demography	
Age, (year)	54 (21-75)**
Female, N (%)	107 (89,9%)
Positive Rheumatoid Factor, N(%)	49 (41,2%)
Duration of RA, (months)	30 (2-162)**
Low education level, N (%)	36 (30,2%)
Domicile outside Jakarta, N (%)	46 (38,7%)
Ethnic	
Java, N (%)	34 (28,5%)
Sunda, N (%)	21(17,6%)
Batak, N (%)	18 (15,1%)
Betawi, N (%)	14 (11,7%)
Minang, N (%)	13 (10,9%)
Chinese, N (%)	7 (5,8%)
Palembang, N (%)	3 (2,5%)
Bangka, N (%)	2 (1,6%)
Ambon, N (%)	2 (1,6%)
Others, N (%)	5 (4,2%)
Aspect of Therapeutic	
Single DMARD, N (%)	81 (68,1%)
Combined DMARD, N (%)	34 (28,6%)
Methotrexate, N (%)	100 (84%)
Sulfasalazin, N (%)	43 (36,1%)
Chloroquin, N (%)	6 (5%)
Leflunomide, N (%)	5 (4,2%)
Steroid , N (%)	55 (46,2%)
Biologic agents, N (%)	2 (1,7%)
Adjuvant analgetics, N (%)	29 (24,4%)
Aspect of Comorbidity	
Dyslipidemia, N (%)	55 (46.2%)
Obesity, N (%)	44 (37%)
Hypertension, N (%)	43 (36,1%)
Diabetes, N (%)	13 (10,9%)
Coronary artery disease, N (%)	7 (5,9%)
Peripheral artery disease, N (%)	3 (2,5%)
Neoplasm, N (%)	18 (15,1%)
Lung Tuberculosis, N (%)	4 (3,4%)
Pneumonia, N (%)	3 (2,5%)
Other infections, N (%)	31 (26,1%)
Other Autoimune disease, N (%)	2 (1,7%)
Chronic liver disease, N (%)	13 (10,9%)
CKD or AKI, N (%)	4 (3,4%)
Other comorbidities , N (%)	83 (69,7%)

*: normal data distribution (mean ±SD); **: not normal data distribution (median, min-max); Low education level: less than high-school level

Table 2. Disease Activity Evaluation

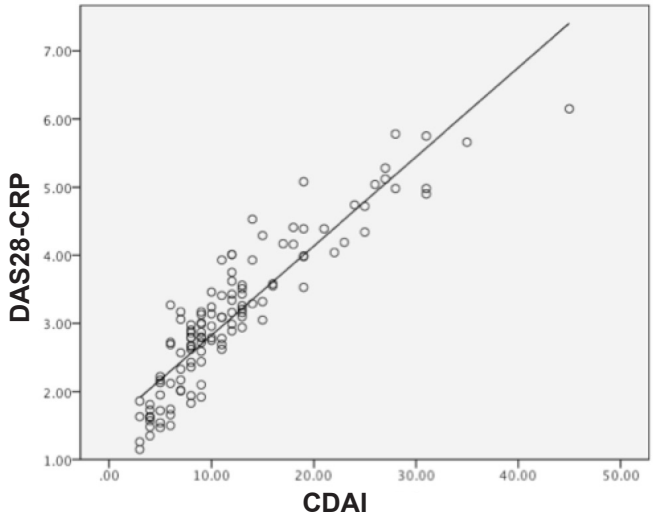
Disease Activity	Results
Clinical	
Sum of tender joints	2 (0-27)**
Sum of swollen joints	0 (0-8)**
Laboratorium	
C-reactive protein (mg/dL)	3,1 (0,1-89,9)**
Erythorcyte sedimentation mate (mm/hour)	43 (4-108)**
Global Assesment	
Patient's Global Assesement DAS28-CRP (0-100)	40 (0-80)**
Patient's Global Assesement CDAI (0-10 mm)	4 (0-8)**
Physician's Global Assesement CDAI (0-10 mm)	4 (0-8)**
Positive Deformity, N (%)	38 (31.9%)

CDAI Score (median,min-max)	10 (3-45)**
DAS28CRP Score (median,min-max)	2,9 (1,15-6,15)**
CDAI Disease Activity Classification	
Remission, N (%)	12 (10,1%)
Low disease activity, N (%)	42 (35,3%)
Moderate disease activity, N (%)	50 (42%)
High disease activity, N (%)	15 (12,6)
DAS 28-CRP Disease Activity Classification	
Remission, N (%)	36 (30,3%)
Low disease activity, N (%)	36 (30,3%)
Moderate disease activity, N (%)	41 (34,5%)
High disease activity, N (%)	6 (5%)

*: normal data distribution (mean ±SD); **: not normal data distribution (median, min-max)

Interclass coefficient correlation revealed *Cronbach's alpha* were 0,999 dan 0,996 (p<0,01). Spearman's Rho =0,918 (p < 0.01); R^2 index= 83,1% (p < 0.01); Adjusted R^2= 82.9% (p < 0.01) Correlation plot were depicted in **Figure 1.**

Figure 1. Correlation Plot of CDAI and DAS28-CRP



DISCUSSION

Clinical disease activity index (CDAI) is a practical approach to asses disease activity which is not requiring any laboratory test. CDAI only incorporates aspects from both physician's and patient's assesement standpoint. This study assesed how well the correlation disease activity assesed by CDAI to other well-established disease activity scoring index, DAS28-CRP. Previous studies which conducted in RA patients without any comorbidities revealed that CDAI and DAS28 has good correlation. We suggested that in RA patients with comobid conditions, the correlation of CDAI and DAS-28 CRP would not work so well since the comobidities may increase CRP values. The increase of CRP values can lead the discrepancy between CDAI and DAS28-CRP, since CDAI does not include CRP value, while DAS28 does.

The rise of CRP does not solely happen due to the increase RA disease activity. Comorbidities, like infections, neoplasm, metabolic degenerative diseases, and other autoimmune diseases, may as well cause the rise of CRP as RA conditions. In daily practice, we rarely encounter patient with single disease entity. We used to treat RA patients with multiple comorbidities. Using CRP as a factor calculated in RA disease activity scoring index might produce bias results, because the rise of CRP is also happened due to the comorbidities condition, with or without any increase in RA disease activity.

In this study we found a positive correlation of CDAI outcomes with DAS28-CRP outcomes. Spearman correlation analysis showed Rho=0,918 (p<0,01). It is revaled that, in assesing RA patients with comorbidites, both CDAI and DAS28-CRP still has good concordance results.

In addition, we also analyzed overall performance of CDAI compared to DAS28-CRP, using R^2 index analysis. In its process, R^2 index analysis is related to linear regression analysis, a technique of fitting lines to data and checking how well the line describes the data. Linear regression examines the relationship between a change in the value of one variabel (predicted) and the corresponding change in the outcome variable (observed). Linear regression is depicted in two axis (X and Y) curve, and relationship between observed and predicted is summarized as a diagonal line. Conclusion drawn from linear regression analysis is stronger and deeper than correlation analysis. While correlation analysis measure only the strength and direction of association between two variables. We cannot interpret further whether the association is predictive or causative, since correlation analysis only shows how well two variables relate to each other. On the other hand, linear regression analysis reflects not only relationship between two varibles but it can also explain predictive and causative aspect between two variables, as the regression line is determined as the best way to predict the outcome of Y from the X. So at the end, conclusions drawn from linear regression analysis are more ready-to-apply in daily clinical practice, than conclusions drawn from correlation analysis. [22-26]

The R^2 index implies how well CDAI outcome could reflect DAS28-CRP outcome. We use DAS28-CRP as comparator because we consider DAS28-CRP as the most comprehensive score, which combines aspect of evaluation from physician's, patient's and laboratory standpoint. Moreover, DAS28-CRP is one of the oldest and earliest score developed by EULAR.[27-28] If we looked back in 1990 when EULAR first described DAS as a measure to asses disease activity, using extensive joints count. Along with its development, EULAR had been frequently remodifying DAS into DAS 4 variables, then DAS 3 variables, until it becomes DAS28-CRP as we know today.[27-29] Revision were subjected to the development of DAS score along with invention and development of new scientific proofs. A score that frequently revised/remodified can be considered comprehensive enough, so that is way we use DAS28-CRP as gold standard.

Correlation/calibration plot (Figure 1) shows a diagonal line which is a best-fit model that can predict outcome of Y

axis (DAS28-CRP) from outcome of X axis (CDAI). In other words, a regression line is also called the line of best fit because it is the line that best represents the pattern of the relationship between the dependent variable and the independent variable. The formula of best-fit line can be determined by equation of y=a+b(x), *a* represent the point where the regression line crosses the Y axis, called the intercept (the value of Y when X is zero) , while *b* represent the slope of the regression line, indicating how much the Y value changes when there is a one-unit change in the value of X. It indicates the strength of the relationship between X and Y (the regression coefficient).

In the statistic analysis of SPSS 23, the we can instantly get the number for a and b. In this study, a = 1,517 and b=0,131, so by using equation of Y=a+b(X), *predictor equation* of CDAI is Y= 1,51 + 0,13(X). [22-25]

Once we identify the regression line, it is important to assess how well it predicts an outcome from the basis of a known variable. (outcome of DAS28-CRP from the basis of CDAI). From the scatterplot (Figure 1) we can see dispersion of the points will affect how accurate the estimate is likely to be. With this predictive model, we calculate a R^2 (coefficient of determination) to measure how much is the variance of DAS28-CRP explained by the variance of CDAI. The R^2 index may vary from 0 to 1. The closer R^2 to 1, means the better prediction model is. While R^2= zero, that means none of the variance is shared between the two variables, both variables are completely unrelated. [22-25] This study reveals that R^2 index index of CDAI is very good (83.1%), since R^2 index >64% is considered very good.

Aside from R^2, there is also adjusted R^2 . Adjusted R^2 is the value of R^2 when the sample size is small, because an estimate of R^2 obtained when the sample size is small tends to be higher than the actual R^2 in the population. The adjusted R^2 is reported only when it substantially differs from R^2 . In this study, the adjusted R^2 = 0,829 (82,9%) . Since the difference between R^2 and adjusted R^2 = 0,829 very small (0.002). Therefore, we can report the R^2 . Given the fact that there is small difference between R^2 and adjusted R^2, also show that the number of samples recruited in this study is adequate. [20,22-25.]

This study revealed that CDAI has good performance in assesing disease activity, even without incorporating CRP value. This finding is in line with the conclusion from study conducted by Aletaha, et al,[3] which said CRP contribute small proportion (15%) to overall DAS28-CRP composition. The equation of DAS28-CRP is as follow: 0,56√tender joint counts + 0,28 √swollen joint counts + 0.36 ln (CRP+1) + 0,014(patient's global assesement)) +0,96. While the equation of CDAI is as follow: tender joint counts + swollen joint counts+ patient's global assesement+ physician's global assesement. From that equation, we can see that CRP component in DAS28-CRP is purposefully reducted by log linear calculation. This has implication in reducing CRP contribution to final result of DAS28-CRP. On the other hand, CDAI score has no reduction component for all components calculated to final result. This explain why the omission of CRP componenet in CDAI, do not interfere its performance in assesing disease activity.

We believe that the reduction of CRP contribution in overall DAS28-CRP calculation, has a deep scientific and logical reasoning. In vitro pathogenesis of RA reveals that progression of joint erosion and joint deformity is happened because of the work of spesific cells and cytokines cascades, named Matrix Metalloproteinase (MMP)-1, MMP-3, Epidermal Growth Factor, VCAM, VEGF, YKL-40, Lymphocyte T, IgM Rheumatoid Factor, Antibodi Anti-Cyclic Citrullinated Protein (AntiCCP), Tumor Necrosis Factor (TNF), IL-6, IL-8, IL-17, RANKL. While CRP is not a spesific acute phase reactant, it is produced by liver and adipocyte, and does not play significant roles in the process of joint erosions, joint destructions, and deformities. Secretion of CRP, as part of innate immunity mechanism, happens generally, not only because of RA activity, but also due to other conditions, such as infections, metabolic diseases, neoplasm, degenerative diseases, and other inflammatory conditions. [30,31]

CDAI has good performance in assesing disease activity in RA patients with or without any comorbidities. Using CDAI, clinicians can perform periodical disease activity evaluation without performing or waiting for any laboratory test (CRP). It can be implicated that CDAI is more time and cost-efficient for clinicans in making theraupetical decision. Clinicians can easily calculate the CDAI score because the formulation is more simple than the formulation of DAS28-CRP. With those reasons, CDAI are allowed to be delivered to all RA patients, both in rural and urban area, or in limited and advanced healthcare resources.

CONCLUSION

Clinical disease activity index has good correlation outcome compared with DAS28-CRP in measuring disease activity of Indonesian RA patients.

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