The relationship between increased levels of Anti-dsDNA with clinical manifestation in patients with SLE in Haji Adam Malik General Hospital Medan

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Abstract. Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease characterized by widespread inflammation and affects any organ system in the body. Many autoimmune diseases result in autoantibody production, but Anti-dsDNA antibodies are highly specific to SLE. Previous study found that Anti-dsDNA antibodies are associated with severe clinical manifestations of lupus. The aim of this study was to examine the relationship between anti-dsDNA level with clinical features and laboratory findings in SLE patients. This cross-sectional study was conducted in Hospital Haji Adam Malik Medan in May-October 2016. We examine anti-dsDNA, clinical features and kidney laboratory profile in all patient. Data were statistically analyzed. 81 SLE patients with median level of anti-dsDNA 294 (6.1-1317). There was no significant relationship between increased level of Anti-dsDNA with clinical manifestations (p>0.05). There were significant relationships between increased level of Anti-dsDNA with renal impairment (p=0.049), urea level (p=0.016), urine protein (p=0.042) and hematolgy disorder (p=0.005). Arthritis is the most frequent clinical manifestation (96.3%) followed by malar rash (77.8%). Elevated anti-dsDNA level was not related with clinical manifestations but there was significant relationship with hematology disorder, urea, creatinine, and proteinuria in SLE patents.

1. Introduction
Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by autoantibodies against cell nuclei and immune complexes involving many organ systems in the body.\cite{1} In general, the disease affects women more than males with a female to male ratio 12:1, with peak incidence in young women between 15-45 years.\cite{2,3}

SLE can affect various organs, such as kidney, musculoskeletal, nervous, skin, cardiovascular, including oral cavity. SLE known as “The Great Imitator” because it can cause a variety of symptoms that are very similar to the symptoms caused by other diseases, so the diagnosis of SLE is very difficult to uphold.\cite{4}

Anti-double stranded DNA antibodies known as anti-dsDNA are one of the specific markers for SLE.\cite{5} This is because it has a high frequency (between 70-98%) with good sensitivity and specificity (67.3 % and 97.4%). The presence of these autoantibodies can directly help to diagnose SLE.\cite{5,6}
Literatures suggest that anti-dsDNA is strongly associated with renal manifestation disorders, where the collected of these antibodies in renal structures such as glomeruli, subendothelial, subepithelial, mesangium, basal membrane and tubules leads to active nephritis in SLE patients. Increased serum anti-dsDNA levels can lead to relapse of SLE, exacerbation of renal disorder, and monitor severity of SLE.[7,8]

Based on the above information, in this study, researchers will evaluate the increase of anti-dsDNA levels against the manifestation of clinical and laboratory symptoms in SLE patients.

2. Methods

2.1. Patient Selection
This study was using analytical research methods with cross-sectional study design, conducted at the General Hospital Haji Adam Malik Medan in May-October 2016. The samples were taken with total sampling technique. All sample were patients diagnosed by the American College of Rheumatology (ACR) 1997 revised criteria for the classification of SLE [9]. Inclusion criteria was SLE patient with flare (MEX SLEDAI >5). We examined clinical features of SLE, Anti-dsDNA level, hemoglobin (Hb), white blood cell count (WBC), thrombocyte and kidney laboratory profile (urea and creatinine) from all patient’s blood serum and urine protein from patient’s urine sample. This study was approved by local ethics committee.

2.2. Statistical Methods
Data analysis was performed through univariate and bivariate analyses using the SPSS 22nd version (SPSS Inc., Chicago) with a 95% confidence interval. Bivariate analysis was performed using Mann-Whitney U test with significance p<0.05.

3. Result
This study was followed by 81 subjects of SLE who had fulfilled the inclusion and exclusion criteria at RSUP H. Adam Malik Medan. The number of women sample were 72 people (88.9%) and men were 9 (11.1%) with the median age of 28 years. The most common clinical manifestation was arthritis as much as 78 (96.3%), rash 63 (77.8%) and photo sensitivity 33 (40.7%).The median level of anti-dsDNA was 294 (6.1-1317),(Table 1)

| Characteristics                  | N      |
|----------------------------------|--------|
| Age (years)                      | 28 (15-64)* |
| Sex                              |         |
| Men                              | 9 (11.1%)* |
| Women                            | 72 (88.9%)* |
| Clinical Manifestation            |         |
| Malar Rash                       | 63 (77.8%)* |
| Discoid rash                     | 23 (28.4%)* |
| Fotosensitivity                   | 33 (40.7%)* |
| Oral Ulcer                       | 29 (35.8%)* |
| Artritis                         | 78 (96.3%)* |
| Serositis                        | 23 (28.4%)* |
| Renal impairment                 | 27 (33.3%)* |
| Neurologic disorder              | 5 (6.2%)* |
| Hematology disorder              | 55 (67.9%)* |
| Elevated urea level              | 24 (29.6%)* |
| Elevated creatinin level         | 15 (18.5%)* |
| Protein Urinary                  | 14 (17.3%)* |
| Anti-dsDNA levels                | 294 (6.1-1317)* |
In this study, a Mann-Whitney U test showed that there were significant relationships between increased anti-dsDNA level with renal impairment (p = 0.049), hematologic disorders (p = 0.005), urea (p = 0.016), and urine protein (p = 0.042) in SLE patients. (Table 2)

**Table 2.** The relationship between basic characteristics of subjects, clinical manifestations, and laboratory against levels of Anti-dsDNA.

| Variable                  | Anti ds-DNA level (Mean±SD) | p   |
|---------------------------|----------------------------|-----|
| Sex                       |                            |     |
| Men                       | 239.42±122.1               | 0.21|
| Women                     | 462.93±384.9               |     |
| Malar Rash                |                            |     |
| Yes                       | 453.4±379.3                | 0.674|
| No                        | 384.52±347.3               |     |
| Discoid Rash              |                            |     |
| Yes                       | 346.5±368.9                | 0.104|
| No                        | 474.3±369.3                |     |
| Photosensitivity          |                            |     |
| Yes                       | 456.3±428.3                | 0.889|
| No                        | 425.57±331.1               |     |
| Oral Ulcer                |                            |     |
| Yes                       | 469.66±358.65              | 0.503|
| No                        | 420.49±380.7               |     |
| Arthritis                 |                            |     |
| Yes                       | 438.89±377.6               | 0.68 |
| No                        | 417.33±170.47              |     |
| Serositis                 |                            |     |
| Yes                       | 445.66±409.7               | 0.929|
| No                        | 435.09±359.0               |     |
| Renal impairment          |                            |     |
| Yes                       | 554.24±381.5               | 0.049a|
| No                        | 380.02±355.8               |     |
| Neurologic disorder       |                            |     |
| Yes                       | 440.6±371.8                | 0.969|
| No                        | 437.9±373.9                |     |
| Hematologic disorder      |                            |     |
| Yes                       | 519.84±384.9               | 0.005a|
| No                        | 265.17±275.15              |     |
| Urea                      |                            |     |
| Increased                 | 572.40±384.9               | 0.016a|
| Normal                    | 381.54±353.9               |     |
| Creatinine                |                            |     |
| Increased                 | 564.51±375.7               | 0.09 |
| Normal                    | 409.36±367.3               |     |
| Protein Urine             |                            |     |
| Yes                       | 627.13±389.4               | 0.042a|
| No                        | 398.57±358.1               |     |

*aSignificant p<0.05

In SLE patients with hematologic disorders, there is a difference Anti-dsDNA level in the group with hematological disorders and without hematological disorder that were 519.84 ± 384.9 and 265.17 ± 275.15.
275.15. In SLE patients with renal impairment, it was found that the mean difference of Anti-dsDNA level was 554.24 ± 381.5 in renal impairment and 380.02 ± 355.8 in without renal impairment. (Figure 1)

![Figure 1](image-url)

Figure 1. Box plots Anti-dsDNA levels in patients with SLE group (a) Hematology disorder, (b) renal impairment.

4. Discussion
This study obtained the most common clinical manifestations in patients with SLE was arthritis (96.3%), malar rash (77.8%) and photo sensitivity (40.7%). This result was in line with the study by Narayanan et al. (2010) where musculoskeletal symptoms (arthritis) was the most common clinical presentation in lupus with flares of 90% of cases [10]. Other studies in Southeast Asia by Salido and Reyes (2010) also received generalized manifestations of mucocutaneous lesions (52-98%) and followed by arthritis / musculoskeletal (36-95%). Arthritis was the most common sign in SLE patients.[11]

The emergence of anti-dsDNA by some researchers is associated with the clinical status of patients with particularly severe characteristics involving renal involvement and predicting relapse rates [12,13] but not associated with cutaneous manifestation such as subacute cutaneous lupus or discoid lupus [14]. The median value of anti-dsDNA are 294 (6.1-1317). There is no correlation between Anti-dsDNA level and clinical manifestations (p> 0.05) but this study found a significant relationship between increasing Anti-dsDNA levels with laboratory parameters such as urea level (p= 0.016), impaired renal function (p = 0.049), urine protein (p = 0.042) and hematology disorder (p=0.005).

This study in line with other study conducted by White et al. (1998) in which there is no correlation between Anti-dsDNA and clinical manifestation such as arthritis and rash (p>0.05).[15] Other study by Fabrizio et al. (2015) in which evaluation of 393 patients with SLE in Italy found positive Anti-dsDNA in 62.3% of patients and the manifestation of the kidneys was significantly associated with a positive Anti-dsDNA value (p = 0.001).[12]

In another study by Manhal et al (2016), the results were obtained in line with this study where there was a significant difference between the increase of Anti ds-DNA levels on blood urea (p = 0.041). So from this result it can be said that the increase of Anti-dsDNA levels associated with kidney disorders but still limited role in relation to clinical manifestations.[16]
The limitation of this study was the sample size was small, further research is required with larger samples.

5. Conclusion
The most common clinical manifestations in SLE patients were arthritis (96.3%) followed by malar rash (77.8%), and photosensitivity (40.7%). Elevated anti-dsDNA level was not related with clinical manifestations but there was significant relationship with hematolgy disorder, urea, creatinine, and proteinuria in SLE patients.

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