The Correlation between Serum C3 and C4 Complement Levels with Disease Activity of Systemic Lupus Erythematosus Patients in Dr. Soetomo Hospital, Surabaya

Istiana Hairiah Abas¹, Betty Agustina Tambunan²*, Awalia³

¹Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital Surabaya, Indonesia.
²Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga
³Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Hospital Surabaya, Indonesia.

ABSTRACT

Introduction: The Systemic lupus erythematosus (SLE) is an autoimmune disease that results in inflammation and tissue damage. SLE often creates difficulties in the diagnosis and assessment of disease activity. Disease activity is important as a basis for selecting the appropriate therapy. In addition to clinical SLE, supporting investigations are needed to determine disease activity, one of which is complement examination. Complement plays an important role in autoimmune disease and thought to mediate tissue damage. This study aimed to analyze the correlation between serum complement C3 and C4 levels with SLE patients’ disease activity in Dr. Soetomo Hospital, Surabaya.

Methods: This study used an observational analytic method with a cross-sectional design. The sampling technique was consecutive sampling. The samples of this study were SLE patients who were treated in the inpatient room and poly rheumatology in January-December 2018 periods. The data were analyzed statistically using the Pearson test.

Results: There were 150 SLE patients, most of whom were women (90.0%) with mean age of 29.01±9.8 years. Most levels of complement were low levels (C3 = 48.0% and C4 = 50.7%). Most disease activities were severe flares (44.7%). Results of the Pearson test complement C3 with disease activity were p =0.001, and level of correlation was r =-0.287. However, results of the Pearson test complement C4 with disease activity were p =0.026, and level of correlation was r =-0.182.

Conclusion: There is negative correlation between C3 and C4 complement levels with disease activity of SLE patients in Dr. Soetomo Hospital, Surabaya, which is significant, weak and opposite.

Keywords: Complement levels, Disease activity, Systemic lupus erythematosus

INTRODUCTION

The systemic lupus erythematosus (SLE) is a systemic autoimmune disease that results in chronic inflammation, tissue damage, and diverse presentation of the disease course (Qu et al., 2018). The Lupus Foundation of America states that around 5 million people worldwide are affected by lupus, and there are 16,000 new cases reported each year (The Lupus Foundation of America, 2013). In 1998, there were only 586 lupus sufferers in Indonesia, and in 2005 there was an increase to 6,578 sufferers. Meanwhile, in April 2009, there were 8,891 lupus sufferers, and 15 died (Judha and Setiawan, 2015). Based on SIRS data for 2017 listed in the data and information center, there were 2,166 hospitalized patients diagnosed with lupus from the total of 858 hospitals that reported their data. Kementrian kekesian reported an increase in cases of SLE. In 2016, it increased 2 times compared to 2014 (Kementrian Kesehatan, 2017). SLE often creates difficulties in diagnosis and assessment of disease activity. Thus, investigations are needed to determine the prognosis of the disease. Investigations that can prove autoimmune in the patient, one of which is the serum complement immunology examination. Complement is compound in the blood involved in the immune system (Gandino et al., 2017). Complement exists in the circulation in an inactive state and can be activated via three routes: the classical route, the alternative route, and the lectin pathway. The dominant pathway for complement activation in SLE is the classic route. When there is the activation of SLE disease, complement levels can be measured by the radial immunodiffusion method (Hikmah and Prihaningtyas, 2018).

SLE can affect any tissue with mild to severe levels of symptoms. Assessment of disease activity is critical to assist in the management of SLE patients. Therefore, it is necessary to measure disease activity changes by looking at all possible manifestations (Feld and Isenberg, 2014). Several scoring systems can assess SLE activity, one of which is the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). SLEDAI is considered the easiest scoring system to use in its application because it has the fewest variables and can be completed in a short time. The SLEDAI assessment has the minimum number of 0 and the maximum of 105 with 24

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variables (Mosca, et al, 2007; Mikdashi and Nived, 2015).

Complement mediates tissue damage and influences the patient’s prognosis. Complement levels will decrease because complement is involved in antibody defense in the tissues associated with increased disease activity. The complement level is normal; SLE tends to be calm. The complement level will decrease due to flares (Hospital for Special Surgery, 2015). C3 is normal when the level is 50 mg/dL-120 mg/dL, and C4 is normal when the serum level is 20 mg/dL-50 mg/dL.

In a study conducted at Chang Gung Hospital, Taiwan, “Serum complement factor I is associated with disease activity of systemic lupus erythematosus” showed a significant negative correlation between complement C3 and C4 with disease activity (r = -0.552 and r = -0.276) (Tseng et al., 2018). Based on this study, this study was conducted to analyze the correlation between complement C3 and C4 levels with disease activity in SLE patients in Dr. Soetomo Hospital, Surabaya. Also, Dr. Soetomo Hospital, Surabaya is a hospital type A owned by the government of East Java Province, which is the final referral hospital for eastern Indonesia so that its patients do not only come from Surabaya.

METHODS

This type of study is retrospective analytic observational with a cross-sectional study design. The independent variable was the complement level of C3 and C4, and the dependent variable was the activity of SLE disease. This study has received ethical approval from the ethics committee (No. 1411/KEPK/VIII/2019). Sampling was done by consecutive sampling.

The inclusion criteria for this study were: 1) Patients diagnosed with SLE based on the criteria for Systemic Lupus International Collaborating Clinics (SLICC) in 2012, 2) SLE patients were treated in the inpatient room and poly rheumatology between January - December 2018, 3) SLE patients had data on complement levels of C3 and C4 in their medical records, and 4) SLE patients were 15-50 years old. The exclusion criteria were patients with congenital hypo-complement urticaria disease which can affect the low levels of complement C3 and C4. Based on these inclusion and exclusion criteria, 150 patients were obtained (Figure 1). Samples information about gender, age, work activity, laboratory tests, risk factors, and comorbidities were obtained from medical records.

Before analyzing the results, the sample was identified based on the SLEDAI scoring system. SLEDAI was used to assess SLE disease activity and the type used was SELENA-SELEDAI. SLE patients’ symptoms and clinical manifestations were taken not far from the day when the complement levels of C3 and C4 were examined so that the results of the study were more accurate. If there is inappropriate data, it will be excluded from the study. Disease activity was divided into 5 groups based on the assessment resultst: remission score 0, mild flare score 1-5, moderate flare score 6-10, severe flare score 11-20, and very severe flare score >20.

The collected data were analyzed using the Pearson test. A p-value of less than 0.05 was considered statistically significant. The value of r: 0-0.25 is considered to have a weak correlation, 0.26-0.50 is considered to have a moderate correlation, 0.51-0.75 is considered to have a strong correlation, and 0.76-1 is considered to have a very strong correlation. SPSS (Statistical Package for Social Sciences) software for Windows version 16 was used for statistical analysis.

RESULTS

Characteristics in patients with SLE

One hundred and fifty SLE patients (135 females and 15 males, Figure 1) with a mean age of 29.01 ± 9.8 years (age range 15–50 years) were enrolled during this study period. Most of the patients did not work. The results of the examination of most complement C3 and C4 levels in SLE patients were low levels and the patient’s activity was in a severe flare phase as shown in Table 1.

Table 1. The Characteristics in patients with SLE

| Characteristics | N   | %  | Mean ± SD (min-max) |
|----------------|-----|----|---------------------|
| Gender         |     |    |                     |
| Men            | 15  | 10,0 |                     |
| Woman *        | 135 | 90,0 |                     |
| Age            |     |    |                     |
| 15-19          | 31  | 20,7 |                     |
| 20-32 *        | 65  | 43,3 | 29,01 ± 9,8(15-50) |
| 33-45          | 42  | 28,0 |                     |
| 46-50          | 12  | 8,0  |                     |
| Work activity  |     |    |                     |
| Yes            | 59  | 39,3 |                     |
| Not *          | 91  | 60,7 |                     |
| Levels of complement C3 |     |    |                     |
| Low *          | 72  | 48,0 | 63,37 ± 42,8 (2-184) |
| Normal         | 61  | 40,7 |                     |
| High           | 17  | 11,3 |                     |
| Levels of complement C4 |     |    |                     |
| Low *          | 76  | 50,7 | 25,09 ± 20,8 (3-91) |
| Normal         | 57  | 38,0 |                     |
| High           | 17  | 11,3 |                     |
| Disease Activity |     |    |                     |

Figure 1. Patients enrollment flow chat
Remission 6 4,0
Mild flare 15 10,0
Medium flare 28 18,7
Several flare * 67 44,7
Very severe flare 34 22,7

14,17 ± 7,7 (0-97)

Mild flare 3 11 1
Medium flare 10 10 8
Several flare 40 23 4
Very severe flare 21 11 2

Table 3 shows that patients in the remission phase are only patients with normal complement C3 or C4 levels. Meanwhile, the flare phase varied and was dominated by the several flare phase with low complement C3 and C4 levels. Mild flares were most common in patients with normal complement levels; moderate flares were most in patients with low and normal complement levels, and very severe flares were most in patients with low complement levels. C3 and C4 had a negative (opposite direction) correlation with disease activity and the level of correlation shown a weak correlation.

Table 4. Correlation between complement C4 and disease activity

| Disease Activity | Levels of complement C4 | Pearson Test |
|------------------|--------------------------|--------------|
| Remission        | 0 6 0                    | p=0.026 r=-0.182 |
| Mild flare       | 5 7 3                    |              |
| Medium flare     | 10 10 8                  |              |
| Very severe flare| 21 11 2                  |              |

DISCUSSION

SLE disease is more commonly known as a disease of adult women of childbearing age; only 10%–20% of cases occur in children (Tseng et al., 2018). Thus, the study was carried out on patients aged 15 to 50 years. Based on the results of the analysis (Table 1), it was found that most patients were female (90.0%). The most patient age range was 20-32 years (43.3%) with the mean age of the subjects was 29.01 ± 9.8 years.

In a study conducted at the First Hospital of Jilin University (Changchun, China), 90 patients involved were 87 female patients and 3 male patients with a mean age of 38 ± 13.9 years (Yuan et al., 2019). Weckerle and Niewold in 2011 stated that the ratio of the incidence of women and men is 9:1. The peak incidence of SLE in their study occurred in women of reproductive age, while men were older (Weckerle and Niewold, 2011). In another study at the Assiut University Hospital, Egypt, 51 female patients (86.4%) were obtained from a total of 59 samples with a mean age of 31.3 ± 10.5 years (Mohamed et al., 2019). Overall studies have been conducted to show the same results. SLE is more common in women so that it occurs in patients of reproductive age. This happened because one of the risk factors for SLE played a role in the disease’s course is hormones. The high risk for women is related to levels of the hormone estrogen so that men have a lower risk (Kementrian Kesehatan, 2017).

Based on the work activity, 59 SLE patients who worked, and 91 patients did not. Patients did not work because some of them stop working after being diagnosed with lupus. A study in London obtained that SLE patients had poor physical abilities, poor health conditions, low social functioning, and continuous pain impacted by the patient’s activity (Sutcliffe et al., 1999). Another study in Bangkok, Thailand also concluded that SLE is a disease that can experience repeated flares that can limit the patient’s physical activity. Furthermore, SLE disease activity can affect the activities carried out by patients (Chaiaamnuay et al., 2010).

Assessment of disease activity is critical to determine the appropriate management and prognosis of SLE patients. Disease activity in this study was calculated using the SLEDAI scoring system seen from SLE patients’ medical
negative correlation between serum complement C3 and C4 help the immune process/body defense (Kim et al., 2019). Thus, the increasing value evenly distributed between infection and disease activity. C3 and C4 were consistently low in patients who were found that the most complement levels of C3 and C4 in SLE occur in patients with normal complement levels. It was in line with Bertsias et al. (2015) stating that kidney involvement often occurs in 40-70% of SLE patients and is a significant cause of morbidity and hospitalization (Bertsias et al, 2015). A study which aims to describe the clinical and immunological characteristics of SLE in Arab, found the most common symptoms and clinical manifestations are arthritis or arthralgia followed by anemia, fatigue, malar rash, and kidney manifestations (Adwan, 2019). Thus, further examination is needed for SLE patients using urinalysis and kidney biopsy. Urinalysis is an essential and effective method of detecting and monitoring disease activity. With the urinalysis method, you can see the levels and effective method of detecting and monitoring disease activity. Further studies are needed with or increasing other manifestations. However, it does not rule out that SLE patients with strenuous activity have normal or above normal complement levels. The cause of inflammation in the SLE is not only due to complement but also due to other causes. At Washington University School of Medicine, 159 patients were diagnosed with lupus and showed a correlation between C3 levels and levels of disease activity and clinical changes in disease activity. C3 levels in patients with active disease are lower than those in inactive disease (Kim et al., 2019). Meanwhile, a study in London did not show a correlation between complement C4 and disease activity. The low levels of complement C4 in the SLE patients studied could stem from the ingestion and production of a genetically defective immune system (Senaldi et al., 1988). Decreased levels of complement C4 can be associated with congenital diseases. In individuals with the HLA-B8 (DR3) genetic makeup, C4 levels are low throughout life. If lupus occurs, the C4 level tends to drop more than the baseline level and will continue to show low or normal-low levels regardless of disease activity. Therefore, it is necessary to carry out genetic testing on patients (Sandhu and Quan, 2017).

CONCLUSION
There is a correlation between serum complement C3 and C4 levels with SLE patients’ disease activity in Dr. Soetomo Hospital Surabaya, which is significant, weak, and opposite. Thus, serum complement levels can describe the disease activity of SLE patients. Further studies are needed with a more sophisticated methodology and a larger sample or other variables that are thought to affect the severity of lupus.

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CONFLICT OF INTEREST
The authors declare there is no conflict of interest.

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