INVESTIGATION OF THE ASSOCIATION BETWEEN ANTINUCLEAR ANTIBODIES, ANTI-DOUBLE STRANDED DNA RESULTS AND PERIPHERAL BLOOD CELL INDICATORS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Objectives: To describe the characteristics of antinuclear antibodies **(**ANA) and anti-double stranded DNA **(**anti-dsDNA) results in patients with systemic lupus erythematosus (SLE) and to evaluate the relationship between these results and peripheral blood cell indicators. ***Materials and Methods****:* A retrospective and cross-sectional descriptive study was conducted on 161 patients with a confirmed diagnosis of SLE who were monitored and treated at Hue University of Medicine and Pharmacy Hospital, Hue city from January 2018 to May 2024. ***Results****:* The mean age of the study population was 31.16 ± 13.01 years. The prevalence of SLE in females was 88.2% and was 7.5 times higher than in males. The rates of ANA and anti-dsDNA positivity in SLE patients were 61.5% and 36.6%, respectively. The study population with both positive ANA and anti-dsDNA test results accounted for 32.3%. There was a statistically significant relationship between ANA, anti-dsDNA results, and blood cell indicators including WBCs, neutrophils, lymphocytes, red blood cells, and hemoglobin ($p<0.05$). Additionally, ANA results showed a statistically significant relationship with platelet counts ($p<0.01$). Patients who tested positive for both ANA and anti-dsDNA had the lowest counts of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin compared to other counterparts, with a statistically significant difference ($p<0.01$). ***Conclusion****:* ANA and anti-dsDNA results are statistically significantly associated with peripheral blood cell indicators in patients. It is necessary to consider combining both ANA and anti-dsDNA results to evaluate and predict the disease activity of systemic lupus erythematosus.

Keywords: *ANA, anti-dsDNA, peripheral blood cells, systemic lupus erythematosus.*

I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that affects many organs and tissues of the body, including skin, joints, kidneys, blood vessels, and neurological and hematological systems. The production of autoantibodies and dysregulation of cytokines are prevalent characteristics of the disease. SLE mainly occurs in females aged 15-44, with a female-to-male ratio ranging from 8:1 to 15:1[6]. The disease has a wide range of clinical manifestations, from mild to severe symptoms, and even life-threatening damage due to the severe consequences of the disease. The cause and the pathogenesis of SLE are not fully understood. However, many studies have demonstrated that environmental and genetic factors interact to trigger immune responses leading to the overproduction of pathogenic autoantibodies and dysregulation of cytokines, resulting in tissue and organ damage[5].

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Antinuclear antibodies (ANA) are serological markers that commonly appear in patients with SLE and can be used for screening, diagnosis, and prognosis. ANA tests have high sensitivity, ranging from 95% to 97%, but have low specificity, estimated to be only around 20%[8]. Although the positive ANA result alone cannot diagnose SLE disease, the negative ANA result makes it less likely to have this disease Meanwhile, anti-dsDNA (dsDNA: double-stranded DNA) has a specificity of up to 96% in SLE and is an important immunological criterion according to the SLICC 2012 (SLICC: Systemic Lupus International Collaborating Clinics) and EULAR/ACR 2019 criteria (European league against rheumatism/American college of rheumatology). Anti-dsDNA is a marker that closely correlates with disease activity and can change over time. However, its sensitivity in diagnosis is low, ranging from 52% to 70%[8].

Hematological abnormalities are common disorders in patients with SLE and include hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia[4]. These abnormalities are part of the diagnostic criteria for SLE according to the SLICC and EULAR/ACR criteria. In Vietnam, there have also been several studies describing hematological abnormalities in patients with SLE. However, the results among studies are heterogeneous. Furthermore, there are limited studies on the relationship between ANA and anti-dsDNA results with hematological disorders and no study has evaluated the combination of both ANA and anti-dsDNA results in SLE. Therefore, we conducted the study with two aims:

1. To describe the characteristics of ANA and anti-dsDNA results in patients with SLE.

2. To investigate the association between ANA, anti-dsDNA results, and peripheral blood cell indicators in patients with SLE.

II. MATERIALS AND METHODS

2.1. Study population and design

A retrospective and cross-sectional descriptive study was conducted on SLE patients who were monitored and treated at Hue University of Medicine and Pharmacy Hospital, Hue city from January 2018 to May 2024. A total of 161 patients were recruited for this study. Inclusion criteria for this study were: patients were diagnosed with SLE according to the SLICC 2012 and EULAR/ACR 2019 criteria, and were indicated for ANA, anti-dsDNA, and complete blood count tests. The exclusion criteria of the study included participants who had not been diagnosed with SLE, evidence of pregnancy in female patients, infection, cancer, and other autoimmune diseases such as rheumatoid arthritis and ankylosing spondylitis. Additionally, patients with SLE who did not undergo a full range of tests, including ANA, anti-dsDNA, and complete blood count tests were excluded.

2.2. Research facilities

The TECAN Sunrise, Australia was used to measure optical density (OD: Optical density) for serum samples of patients with SLE who are assigned to test for ANA and anti-dsDNA using the ELISA technique (ELISA: Enzyme-linked Immunosorbent assay) at the Department of Immunology, Hue University of Medicine and Pharmacy Hospital.

The Sysmex XN-550, Japan was also used to perform complete blood count tests of SLE patients at the Department of Hematology-Blood Transfusion, Hue

University of Medicine and Pharmacy Hospital.

2.3. Data collection

2.3.1. Common variables

Population characteristics of patients with a confirmed diagnosis of SLE, including age and gender were recorded.

2.3.2. Laboratory variables

Serum samples from SLE patients were used to detect the presence of ANA and anti-dsDNA using the ELISA technique with chemical kits from DIA.PRO, Italy. The ELISA procedure was carried out following the manufacturer's instructions. The sample/cut-off (S/Co) ratios of ANA below 0.8 **were considered negative; between 0.8 and 1.1 were considered equivocal, and above 1.1 were considered positive.** The levels of anti-dsDNA below 25.0 IU/ml were considered negative, and above 25.0 IU/ml were considered positive.

Additionally, the whole blood samples of SLE patients were used to perform complete blood count tests. The results for peripheral blood cell indicators, including total white blood cells (WBCs), neutrophils, lymphocytes, red blood cells (RBCs), hemoglobin, and platelet counts, were collected. Based on these results, SLE patients were identified as having hematological disorders, including anemia, leukopenia (WBCs < 4 G/l), lymphopenia (lymphocytes < 1 G/l), neutropenia (neutrophils < 1.5 G/L), and thrombocytopenia (platelets <100 G/l).

2.3.3. Data collection steps

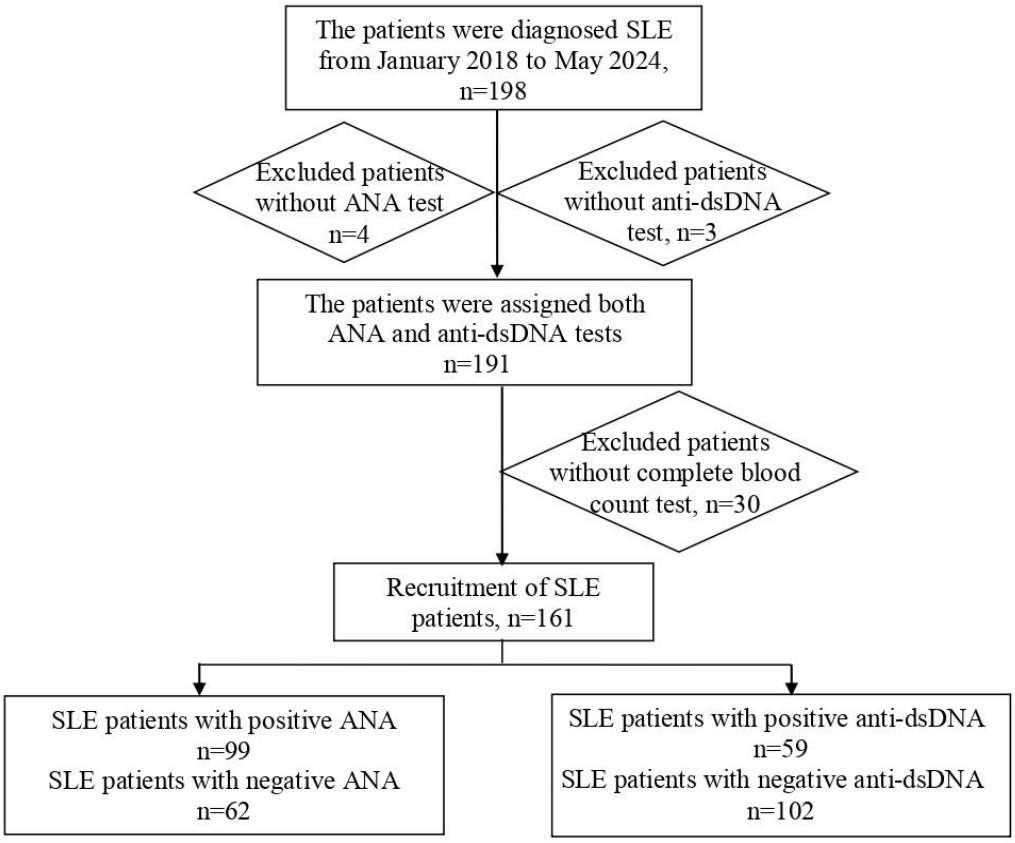

Figure 1: ***Data collection steps and group classification***

2.4. Data analysis

The collected data were analyzed using medical statistical algorithms and SPSS 20.0 software. Variables were shown as numbers, percentages, mean, and standard deviation. The chi-square test was used to evaluate the association between anti-dsDNA and ANA test results as well as their associations with other variables. A *p*-value <0.05 was considered significant in the statistical analyses.

2.5. Ethics

The data in the study were collected retrospectively at the Department of Immunology and Department of Hematology and Blood Transfusion of Hue University of Medicine and Pharmacy Hospital, Hue city where tests were performed for SLE patients. All research subject information was encrypted for confidentiality and used exclusively for research purposes.

III. RESULTS

Table 1: ***Age characteristics of the study population***

Age groups	**n**	**%**
<20	26	16.1
20 - <40	95	59.0
≥40	40	24.8
Total	**161**	**100.0**
Mean ± SD	31.16 ± 13.01	
Oldest age	69	
Youngest age	11	

The mean age of SLE patients was 31.16 ± 13.01 years, ranging from 11 to 69 years old. The majority of SLE patients (59.2%) were aged between 20 and 40 years.

Table 2: ***Gender characteristics of the study population***

Gender	**n**	**%**
Female	142	88.2
Male	19	11.8
Total	**161**	**100.0**

The prevalence of females with SLE accounted for 88.2% and a female-to-male ratio of 7.47:1.

Table 3: ***Characteristics of peripheral blood cell indicators***

Blood cell indicators	**Mean ±SD**	**Lowest**	**Highest**
WBCs (G/L)	7.2 ± 3.4	1.9	17.6
Neutrophils (G/L)	4.6 ± 3.1	0.5	24.6
Lymphocytes (G/L)	2.1 ± 1.1	0.4	7.4
RBCs (T/L)	4.1 ± 0.6	2.6	6.1
Hemoglobin (g/L)	117.3 ± 18.1	73.2	181.0
Platelets (G/L)	252.1 ± 86.8	11.0	583.0
Total	**161**		

The mean results of WBCs, RBCs, and PLTs in SLE patients were 7.2 ± 3.4 G/L, 4.1 ± 0.6 T/L, and 252.1 ± 86.8 respectively. The mean of hemoglobin concentrations in these patients was 117.3 ± 18.1 g/L.

Table 4: ***Characteristics of disorders of blood cell indicators***

Disorders of blood cell indicators		n	%
Anemia	Severity level (Hb: < 60 g/L)	0	0
	Medium level (Hb: 60 - < 90 g/L)	10	6.2
	Mild level (Hb: 90 - < 120 g/L)	78	48.4
	Total	**88**	**54.6**
Thrombocytopenia	platelets < 100 G/l	7	4.3
Leukopenia	WBCs < 4 G/l	22	13.7
Lymphopenia	Lymphocytes < 1G/l	21	13.0
Neutropenia	Neutrophils < 1.5 G/l	10	6.2

The rate of anemia in SLE patients was 54.6%, with mild anemia accounting for the highest proportion rate at 48.4%. The rate of thrombocytopenia was 4.3%. Additionally, the rates of leukopenia, lymphocytosis, and neutropenia were 13.7%, 13.0%, and 6.2%, respectively.

Table 5: ***Characteristics of ANA and anti-dsDNA results***

ANA and anti-dsDNA results		n	%
ANA	Positive	99	61.5
	Negative	62	38.5
	Total	**161**	**100.0**
Anti-dsDNA	Positive	59	36.6
	Negative	102	63.4
Total		**161**	**100.0**
Combination group of ANA and anti-dsDNA	Both negative ANA and anti-dsDNA	55	34.2
	Positive ANA and negative anti-dsDNA	47	29.2
	Both positive ANA and anti-dsDNA	52	32.3
	Negative ANA and positive anti-dsDNA	7	4.3
Total		**161**	**100.0**

The rates of positive ANA and anti-dsDNA results in patients were 61.5% and 36.6%, respectively. The rate of both positive ANA and anti-dsDNA results was 32.3% among the 161 SLE patients.

Table 6: ***Association between ANA results and blood cell indicators***

	ANA		*p*-value
	Negative	**Positive**	
WBCs (± SD) (G/L)	8.7 ± 3.6	6.3 ± 2.8	**0.000**
Neutrophils (± SD) (G/L)	5.8 ± 3.9	3.9 ± 2.2	**0.001**
Lymphocytes (± SD) (G/L)	2.6 ± 1.2	1.8 ± 1.0	**0.001**
RBCs (± SD) (T/L)	4.4 ± 0.6	4.0 ± 0.6	**0.000**
Hemoglobin (± SD) (g/L)	122.2 ± 18.7	114.1 ± 17.1	**0.006**
Platelets (± SD) (G/L)	274.8 ± 87.5	237.8 ± 83.6	**0.008**
Total	**62**	**99**	

There were associations between ANA results and the total number of WBCs, neutrophils, lymphocytes, RBCs, hemoglobin concentrations and platelets, with a statistically significant difference ($p<0.01$).

Table 7: ***Association between anti-dsDNA levels and blood cell indicators***

	Anti-dsDNA			*p*-value
	< 25 IU/ml	**≥ 25 - < 100 IU/ml**	**≥ 100 IU/ml**	
WBCs (± SD) (G/L)	7.9 ± 3.5	6.5 ± 2.6	4.7 ± 2.2	**0.000**
Neutrophils (± SD) (G/L)	5.1 ± 3.4	4.1 ± 2.1	3.0 ± 1.7	**0.013**
Lymphocytes (± SD) (G/L)	2.4 ± 1.1	1.8 ± 1.0	1.2 ± 0.6	**0.000**
RBCs (± SD) (T/L)	4.2 ± 0.6	4.1 ± 0.5	3.6 ± 0.6	**0.000**
Hemoglobin (± SD) (g/L)	120.0 ± 17.9	116.8 ± 14.7	101.9 ± 17.5	**0.000**
Platelets (± SD) (G/L)	261.1 ± 91.4	236.0 ± 65.7	225.6 ± 83.4	0.133
Total	**111**	**31**	**19**	

There were relationships between anti-dsDNA levels and total number of WBCs, neutrophils, lymphocytes, RBCs and hemoglobin level with a statistically significant difference ($p < 0.05$).

Table 8: ***Association between both ANA and anti-dsDNA results and blood cell indicators***

	Both negative ANA and anti-dsDNA	**Positive ANA and negative anti-dsDNA**	**Both positive ANA and anti-dsDNA**	**Negative ANA and positive anti-dsDNA**	*p*-value
WBCs (± SD) (G/L)	8.9 ± 3.8	6.9 ± 3.0	5.7 ± 2.6	7.9 ± 2.1	**0.000**
Neutrophils (± SD) (G/L)	5.9 ± 4.1	4.2 ± 2.4	3.6 ± 2.0	5.2 ± 2.3	**0.001**
Lymphocytes (± SD) (G/L)	2.7 ± 1.2	2.1 ± 1.0	1.6 ± 0.9	2.0 ± 0.7	**0.000**
RBCs (± SD) (T/L)	4.3 ± 0.6	4.1 ± 0.6	3.9 ± 0.6	4.6 ± 0.4	**0.002**
Hemoglobin (± SD) (g/L)	121.4 ± 19.1	117.2 ± 16.8	111.4 ± 17.0	128.9 ± 14.4	**0.010**
Platelets (± SD) (G/L)	274.4 ± 87.8	245.9 ± 95.6	230.5 ± 71.2	278.0 ± 92.4	0.051
Total	**55**	**47**	**52**	**7**	

There were associations between the ANA and anti-dsDNA result groups and the total number of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin with a statistically significant difference ($p < 0.01$).

IV. DISCUSSION

Patients with SLE mainly occur in adolescents and young adults. In our study, the average age of 161 patients with SLE was 31.16 ± 13.01 years with the oldest being 69 years old and the youngest 11 years old. The age group from 20 - < 40 years old was the most common, accounting for 59.0% of the SLE patients (Table 1). Vo Tam et al. (2016) studied 55 SLE patients and found that the average age was 33.2 ± 11.4 years[3]. Nguyen Hoang Bac et al. (2023) and Doan Thien Hao et al. (2023) reported the average age of 35.57 ± 11.03 years and 32.54 ± 9.3 years, respectively, in their studies on SLE patients[1,2].

The prevalence of SLE is notably higher in females than in males, especially during the childbearing age. Changes in female sex hormones impact innate and adaptive immune responses, and dysregulation of these mechanisms contributes to the clinical manifestations of SLE. Progesterone and androgens function to fight autoimmune diseases, while estrogen is generally regarded as pathogenic due to its association with genetic and epigenetic changes in SLE. Therefore, estrogen is considered to contribute to the predisposition to SLE[6]. In our study, it was found that 88.2% of patients with SLE were female and only 11.8% of patients were male (Table 2). Nguyen Hoang Bac et al. (2023) showed an incidence rate of 90% among females[1]. Vo Tam et al. (2016) and Doan Thien Hao et al (2023) recorded this incidence of up to 94.5% and 94.2%, respectively[3,2].

The average counts for WBCs, neutrophils, lymphocytes, RBCs, and platelets in 161 SLE patients were 7.2 ± 3.4 G/L, 4.6 ± 3.1 G/L, 2.1 ± 1.1 G/L, 4.1 ± 0.6 T/L and 252.1 ± 86.8 G/ L, respectively. The average hemoglobin concentration was 117.3 ± 18.1 9 g/L (Table 3). Based on the diagnostic criteria of SLICC 2012 and EULAR/ACR 2019, which define hematological disorders in SLE including reduced WBC count (<4 G/L), lymphocytopenia (<1 G/L), and thrombocytopenia (<100 G/L), our study observed rates of 13.7% for decreased WBC count, 13.0% for lymphocytopenia, and 4.3% for thrombocytopenia among 161 SLE patients. Additionally, we found that 54.6% of patients experienced mild to moderate anemia, and 6.2% exhibited neutropenia (Table 4). Vo Tam et al. (2016) reported rates of leukopenia, lymphopenia, and thrombocytopenia as 25.5%, 49.1%, and 16.4%, respectively[3]. Conversely, Doan Thi Thien Hao et al. (2023) observed lower rates of leukopenia (3.8%) and thrombocytopenia (3.8%) in their study involving 52 SLE patients[2].

In our study of 161 patients with SLE, we found positive rates of ANA and anti-dsDNA to be 61.5% and 36.6%, respectively (Table 5). Further analysis revealed that 34.2% of patients tested negative for both ANA and anti-dsDNA, and 32.3% of patients tested positive for both. The lowest proportion, 4.3%, tested negative for ANA but positive for anti-dsDNA. Vo Tam et al. (2016) indicated higher positive rates of ANA (96.4%) and anti-dsDNA (89.1%)[3], whereas Moreno-Torres et al. (2022) recorded rates of 88% for ANA and 38% for anti-dsDNA[7]. The variability in positive ANA and anti-dsDNA results among studies may be due to differences in sample size, patient demographics, race, and methods used to detect ANA and anti-dsDNA.

The values of blood cell indicators in patients with positive ANA were statistically significantly lower compared to those in patients with negative ANA ($p < 0.01$). Specifically, the counts of WBCs, neutrophils, lymphocytes, RBCs, and platelets in the ANA-positive group were 6.3 ± 2.8 G/L, 3.9 ± 2.2 G/L, 1.8 ± 1.0 G/L, 4.0 ± 0.6 T/L, and 114.1 ± 17.1 G/L, respectively. Meanwhile, these indicators in the ANA-negative group were 8.7 ± 3.6 G/L, 5.8 ± 3.9 G/L, 2.6 ± 1.2 G/L, 4.4 ± 0.6 T/L and 274.8 ± 87.5 G/L, respectively (Table 6). Furthermore, the hemoglobin concentration in the ANA-positive group was 114.1 ± 17.1 g/L, significantly lower than in the ANA-negative group, which was 122.2 ± 18.7 g/L ($p < 0.01$) (Table 6). Nguyen Hoang Bac et

al. (2023) also reported a significantly lower RBC count in the ANA-positive group compared to the ANA-negative group ($p < 0.05$). However, there were no significant differences observed in platelet counts and hemoglobin concentrations between ANA-positive and ANA-negative groups ($p > 0.05$) (Table 6)[1].

The anti-dsDNA levels were statistically significantly related to the number of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin concentrations ($p < 0.05$). The results in Table 7 displayed that the higher the anti-dsDNA levels, the lower the value of these indicators. In the group of patients with anti-dsDNA levels ≥ 100 IU/ml, the number of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin concentrations was recorded as the lowest compared to the remaining groups, with values of 4.7 ± 2.2 G/L, 3.0 ± 1.7 G/L, 1.2 ± 0.6 G/L, 3.6 ± 0.6 T/L, and 101.9 ± 17.5 g/L, respectively (Table 7). Nguyen Hoang Bac et al. (2023) also showed a statistically significant difference between anti-dsDNA positive and negative groups in terms of RBC count, hemoglobin concentration, and platelet count[1]. However, in our study, there was no statistically significant difference between anti-dsDNA concentration and platelet count with $p > 0.05$ (Table 7).

We combined the results of both ANA and anti-dsDNA to analyze the association between groups with common variables of blood cell indicators. The results in Table 8 show a statistically significant association between the ANA and anti-dsDNA result groups and hematological indicators, including WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin concentrations ($p < 0.01$). The group with both ANA and anti-dsDNA positive had the lowest values for these hematological indicators compared to the other result groups. Specifically, the values of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin concentrations were 5.7 ± 2.6 G/L, 3.6 ± 2.0 G/L, 1.6 ± 0.9 G/L, 3.9 ± 0.6 T/L, and 111.4 ± 17.0 g/L, respectively. In contrast, the group of patients with both ANA and anti-dsDNA negative had the highest values for WBCs, neutrophils, and lymphocytes, with results of 8.9 ± 3.8 G/L, 5.9 ± 4.1 G/L, and 2.7 ± 1.2 G/L, respectively. The highest values for RBC count and hemoglobin concentration were found in the group of patients with negative ANA and positive anti-dsDNA. Although platelet counts varied among the groups, these differences were not statistically significant ($p > 0.05$) (Table 8).

The pathogenesis of reduced numbers of blood cells is also not fully understood. The humoral immune response and cell-mediated immunity may be involved in the disease's pathogenesis. Some studies suggest that leukopenia is related to the production of the cytokine TNF (TNF: tumor necrosis factor), which activates cell death signals. Antibodies in SLE against RBCs are mainly IgG, which are associated with hemolytic anemia and a positive Coombs test. Additionally, some studies indicate that a deficiency in the expression of certain protein molecules, such as CD55 and CD59 on the surface of RBCs, is also related to hemolytic anemia. However, the exact mechanisms of autoimmune hemolysis in SLE remain unclear[4].

Detection of these antibodies is very useful for predicting disease progression, monitoring treatment effectiveness, and crucially, preventing overlooked cases. However, many studies analyzing ANA and anti-dsDNA in diagnosing and assessing SLE

often consider them separately without evaluating their combined impact. Our study revealed significant, clear changes in blood cell indicators when combining ANA and anti-dsDNA results. Hematological indicators were notably lowest in patients positive for both ANA and anti-dsDNA, which may indicate heightened SLE activity in this group. Nevertheless, a limitation of our study is the absence of analysis regarding how both ANA and anti-dsDNA correlate with clinical features or their relationship with disease activity measured by the SLEDAI scale (Systemic Lupus Erythematosus Disease Activity Index). Additionally, SLE patients taking immunosuppressive medications were not excluded from our study. Therefore, we will continue to research to further clarify the role of ANA and anti-dsDNA when analyzing and combining their results in assessing the disease status of SLE.

V. CONCLUSION

The proportion of patients with positive ANA and anti-dsDNA results among a total of 161 SLE patients was 61.5% and 36.6%, respectively. The proportion of patients with both ANA and anti-dsDNA positive was 32.3%. There was a statistically significant association between ANA results as well as anti-dsDNA results and peripheral blood cell indicators, including WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin concentrations ($p<0.05$). ANA results were also correlated with platelet count ($p<0.01$).

In the group of SLE patients positive for both ANA and anti-dsDNA, the counts of WBCs, neutrophils, lymphocytes, RBCs, and hemoglobin were significantly lower compared to other groups ($p < 0.01$). Therefore, combining both ANA and anti-dsDNA results is essential for the comprehensive assessment and monitoring of SLE status.

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