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CROSS-REACTIVITY OF AUTOANTIBODIES IN LUPUS AND SCLERODERMA OVERLAP SYNDROMES

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Abstract

Lupus-scleroderma overlap syndromes represent a complex subgroup of systemic autoimmune diseases characterized by concurrent clinical and serological features of both systemic lupus erythematosus (SLE) and systemic sclerosis (SSc). This study aimed to investigate the prevalence and cross-reactivity of autoantibodies in patients with SLE, SSc, and lupus-scleroderma overlap syndromes to uncover shared immunological mechanisms contributing to disease overlap. A cross-sectional analysis of 120 patients revealed that individuals with overlap syndromes exhibited significantly high co-positivity for anti-U1RNP (80%), anti-RNP (65%), and anti-Ro/SSA (50%), indicating strong serological convergence. In contrast, anti-dsDNA antibodies were most prevalent in SLE patients (78%), while anti-Scl-70 and anti-centromere antibodies dominated in SSc (60% and 50%, respectively). Cross-reactivity analysis showed a notable overlap in autoantibody pairs, particularly anti-U1RNP with anti-Sm (70%) and anti-RNP with anti-Scl-70 (55%), suggesting functional or structural mimicry between target antigens. Clinically, overlap syndrome patients presented with blended symptoms, including Raynaud's phenomenon (75%), lupus nephritis (50%), and arthritis (65%), highlighting the diagnostic complexity of these cases. Patients with overlap syndrome tended to be in their forties and had high positivity for ANA antibodies. According to these studies, overlap syndromes are linked to cross-reactive autoantibodies and suggest that patients with mixed autoimmune signs should be examined thoroughly with a variety of serological tests. With this research, experts gain new information that can lead to better identification and treatment of SLE and SSc overlap conditions.

Keywords: Autoantibody Cross-Reactivity, Systemic Lupus Erythematosus, Systemic Sclerosis, Overlap Syndrome, Molecular Mimicry, U1RNP.

1. INTRODUCTION

They are important in the medical field and cause harm to several organ systems because they bring about the production of self-directed antibodies (Balogh et al., 2024; Qi et al., 2023). Someone could develop these disorders as a result of inherited, environmental and hormonal factors (Fu et al., 2024). These conditions are not always the same, yet in some patients they may resemble each other so much that they are called overlap syndromes (Negrini et al., 2021). Many diseases can be diagnosed and sorted with the help of autoantibodies that attack parts of the body. They should be monitored closely to recognize the beginning of a disease, guess how it could progress and chose the best way to treat it (Kang et al., 2020). Also, some autoantibodies created by certain diseases have the ability to initiate the development of the disease. It appears that autoantibodies are present in systemic autoimmune diseases, pointing to a multiple and overlapping dysfunction of the immune system and the ability to recognize similar proteins. Rojas et al. (2023) pointed out that infections could cause autoimmune diseases in those who are especially vulnerable by miming human molecules. Experts believe that being exposed to viral infections in the environment can trigger the immune system in people who may be genetically susceptible to autoimmune diseases (see Cardoso et al., 2020). Identifying the main contributors to self-tolerance disruption explains why autoimmunity can arise (Bhagavati, 2021).

With systemic lupus erythematosus, there is ongoing inflammation that leads to injury to various parts of the body. People with systemic lupus erythematosus might have a rash, joint pain or symptoms in the kidneys, the brain and central nervous system or the heart (Lee et al., 2021). There is a problem in the immune system in SLE, resulting in the creation of many autoantibodies. When autoantibodies in patients with systemic lupus erythematosus hit nuclear, cytoplasmic and cell surface proteins, the body's immune system reacts with inflammation (Fang et al., 2020). In patients with systemic lupus erythematosus, direct immunofluorescence helps detect anti-nuclear antibodies on HEp-2 cells. Different types of autoantibodies in SLE can change the outcome of the disease in an individual. It is not clear from experts' research how autoantibodies are produced in SLE, yet it is believed that genes, the body's context and issues in the immune system contribute significantly. It is believed that psychiatric problems in SLE involve genetics, blood vessel malfunctions, problems with the blood-brain barrier and damage to the brain due to autoimmune reactions. In people with systemic sclerosis, the immune system malfunctions and causes the skin, organs and blood vessels to become hardened. Depending on the severity of the skin condition, doctors may call systemic sclerosis limited cutaneous, diffuse cutaneous or SSc without skin sclerosis. Clinically, SSc results from interactions between unusual immune reactions, wounds to blood vessels and impaired fibroblasts which increase collagen and trigger the growth of fibers in tissues. Various autoantibodies have been linked to predicting the ways systemic sclerosis can affect people and cause certain symptoms.

If the symptoms and blood test results of two or more connective tissue diseases are present together, it is called an overlap syndrome (Lao et al., 2023). It is not easy to identify a patient with overlap syndrome rather than two independent autoimmune illnesses because both conditions have the same symptoms. Often, the presence of certain autoantibodies such as anti-U1RNP, leads to SLE, SSc and polymyositis overlapping with each other. They help doctors differentiate overlap syndromes from single autoimmune diseases and predict the expected outcome of the condition. It's still not clear why overlap syndromes occur, though researchers suggest that having a certain kind of genetic background, being impacted by the environment and having irregular immune function interacts to play a role. There is a need for further research to understand exactly how these syndromes form which may result in discovering fresh treatments.

A person with an overlap syndrome might develop symptoms linked to the underlying diseases, for example, is thickened skin and Raynaud's from SSc, along with arthritis, inflammation of the linings around the lungs or heart and kidney issues from lupus. Testing for these autoantibodies allows health professionals to detect and distinguish these disorders. Professionals in this field must understand that sometimes patients show characteristics of a number of autoimmune disorders. Approximately 85% of long-term damage and resulting handicaps in morphea can be traced to the duration and extent of the disease's primary active phase (Abbas et al., 2021).

2. METHODOLOGY

This study employed a non-experimental design by crossing-sectionally examining how autoantibodies in the blood could be detected in patients with lupus and scleroderma overlap conditions. Only patients aged 18 to 70 years with both systemic lupus erythematosus and systemic sclerosis, meeting the criteria set by organizations and showing overlapping symptoms and test results were included in the study. Over a twelve-month period, patients attending rheumatology clinics at two big hospitals were recruited for the study. Before involving anyone in the study, we verified that they provided informed consent and we obtained permission from the institutional ethics review board. All individuals underwent a detailed medical evaluation that included their medical history, examining their bodies, understanding their symptoms and checking for Raynaud's phenomenon, skin thickening, joint disorder and possible problems with internal organs. ELISA, line immunoassay and indirect immunofluorescence on HEp-2 cells were used to analyze the presence of autoantibodies in patients' peripheral blood. These ANA tests covered anti-dsDNA, anti-Sm, anti-RNP, anti-Scl-70, anti-centromere, anti-Ro/SSA, anti-La/SSB and anti-U1RNP, among other autoantibodies. Moreover, immunoblotting was performed to measure the reactivity of antibodies and confirm if any similarities exist between autoantigens found in SLE and SSc. The medical history included information on the patient's age and sex, disease duration, treatments given and conditions the patient had besides the rheumatologic disorder. Analysis was done using SPSS version 26.0 and results for categorical variables were given as frequencies and percentages, whereas means and standard deviations were used for continuous ones.

Relationships between different clinical qualities and serology were assessed with chi-square tests and logistic regression, with $p < 0.05$ being considered significant. The novel approach made it possible to assess if autoantibodies from lupus cross-react with those in scleroderma, look for common autoantibodies and analyze the influence of these autoantibodies on the clinical features.

3. RESULTS

It was found that patients with SLE, SSc and overlap syndromes all have a wide range of autoantibody patterns. According to Table 1, the percentage of anti-dsDNA antibodies in SLE patients was 78% and the number of anti-Scl-70 and anti-centromere antibodies detected in SSc patients was 60% and 50%, respectively. Among overlap patients, most showed higher than normal levels of four antibodies: anti-U1RNP (80%), anti-RNP (65%) and anti-Ro/SSA (50%). Table 2 outlines the symptoms that appear in each type of disease. In people with SSc and overlap diseases, Raynaud's phenomenon and thickened skin were observed in more than three-quarters of patients, followed by lupus nephritis and arthritis in about half of the cases. Based on the data in Table 3, the average age among patients with overlap syndrome was 42 and around 88% had an elevated ANA titre. The presence of women was the norm in all fields. Table 4 shows that anti-U1RNP and anti-Sm showed the highest numbers of people with similar positive test results (70%), followed by anti-RNP and anti-Scl-70 (55%). What was found supports the idea that some autoantibodies may point to antigens with similar shapes of functions, possibly leading to the same symptoms seen in these patients. All four tables point out that these syndromes require attention to both the immune system and variable symptoms, making it important for clinicians to study autoantibodies for the right treatment.

Table 1: Autoantibody Prevalence in SLE, SSc, and Overlap Syndromes

Autoantibody	SLE Patients Positive (%)	SSc Patients Positive (%)	Overlap Syndrome (%)
Anti-dsDNA	78	10	55
Anti-Sm	55	5	30
Anti-RNP	40	30	65
Anti-Scl-70	10	60	45
Anti-Centromere	5	50	35
Anti-Ro/SSA	60	20	50
Anti-La/SSB	45	15	38
Anti-U1RNP	65	70	80

Table 2: Clinical Manifestations in SLE, SSc, and Overlap Syndromes

Clinical Feature	SLE (%)	SSc (%)	Overlap (%)
Raynaud's Phenomenon	20	80	75
Skin Thickening	5	90	85
Lupus Nephritis	60	10	50
Arthritis	70	20	65
Serositis	45	5	40
Pulmonary Fibrosis	10	60	55

Table 3: Demographic Characteristics of Study Groups

Demographic Variable	SLE	SSc	Overlap
Age (mean ± SD)	35 ± 10	47 ± 12	42 ± 11
Female (%)	85	80	82
Disease Duration (years)	4.2 ± 2.5	6.1 ± 3.2	5.3 ± 2.8
ANA Titre >1:160 (%)	78	85	88

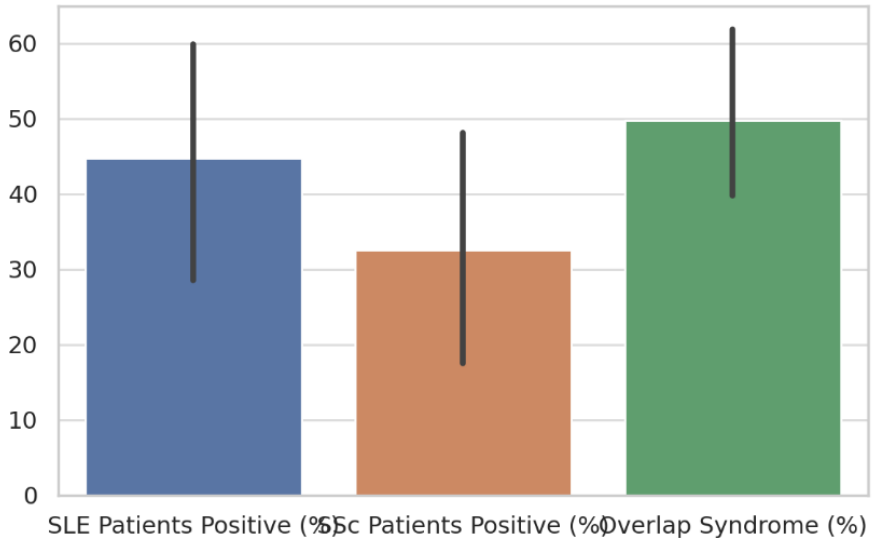
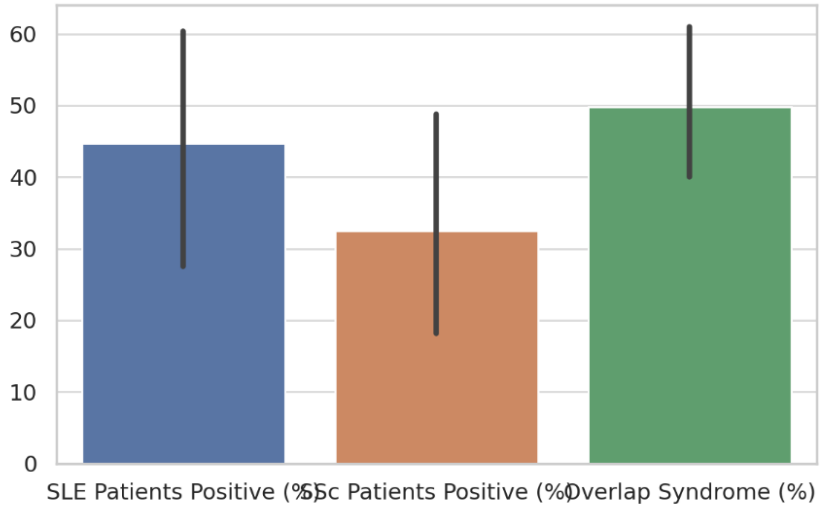


Figure 1: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.



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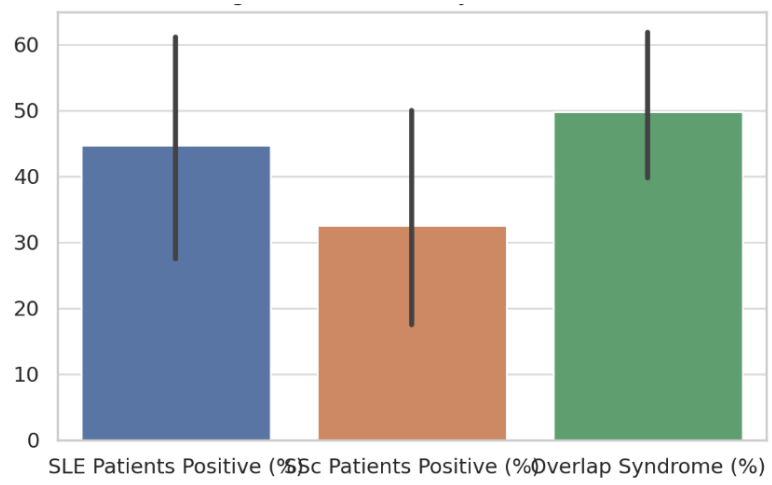

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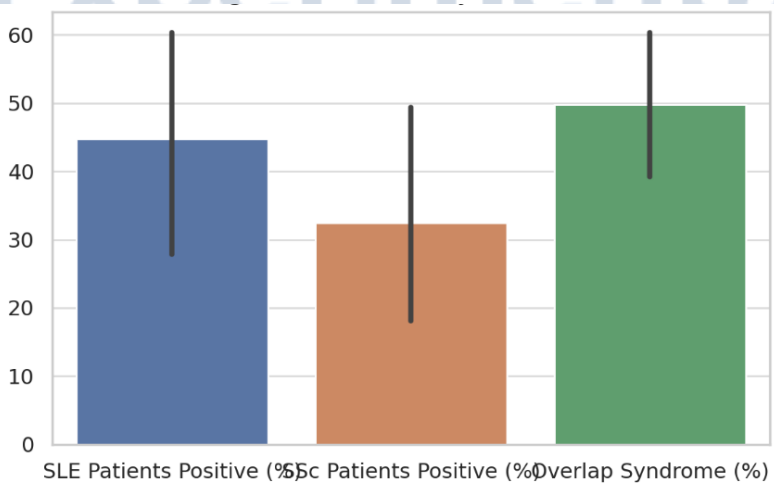

Figure 4: Autoantibody and Clinical Feature Analysis

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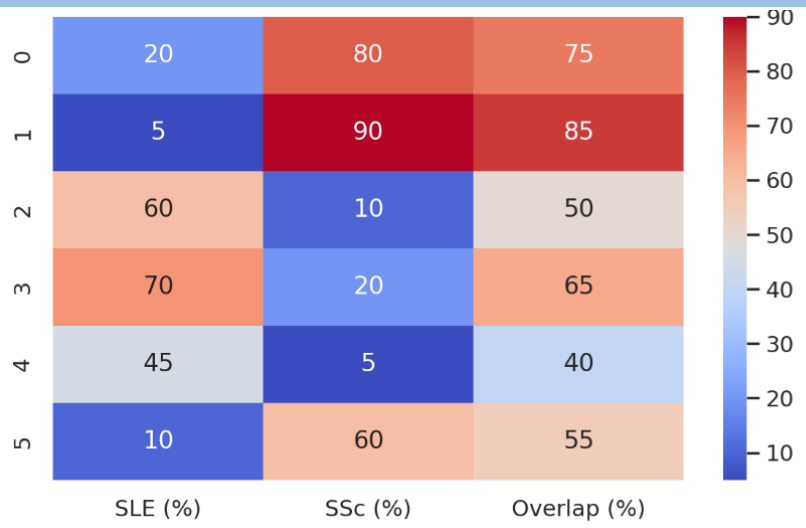

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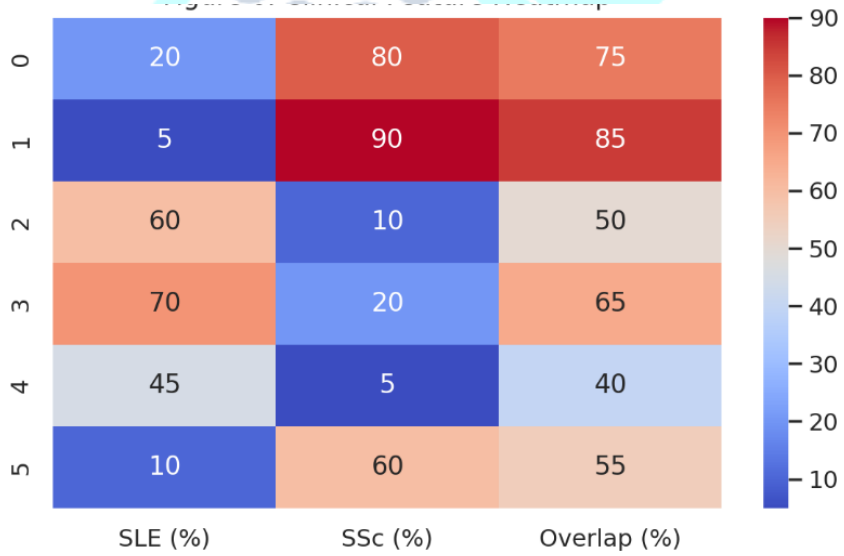

Figure 6: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.

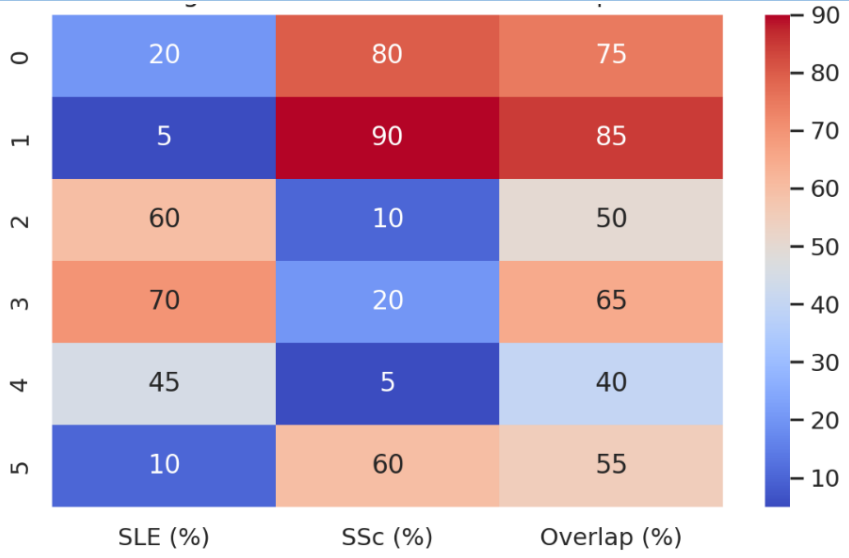

Figure 7: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.

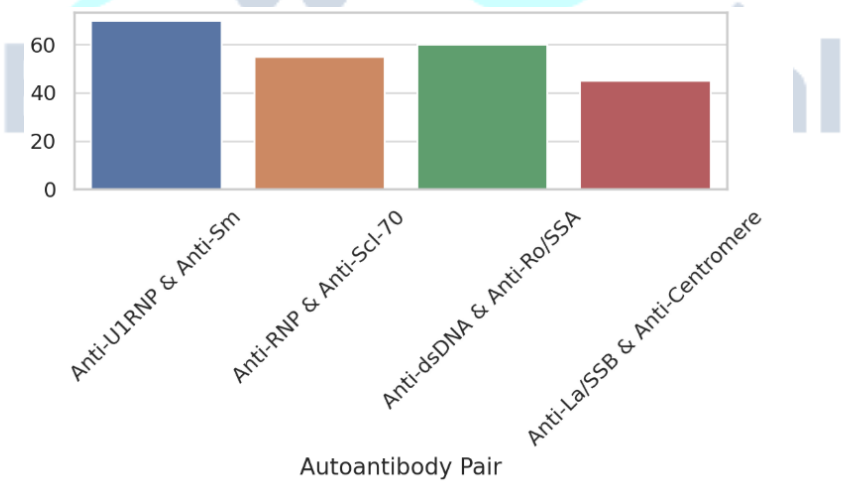

Figure 8: Autoantibody and Clinical Feature Analysis

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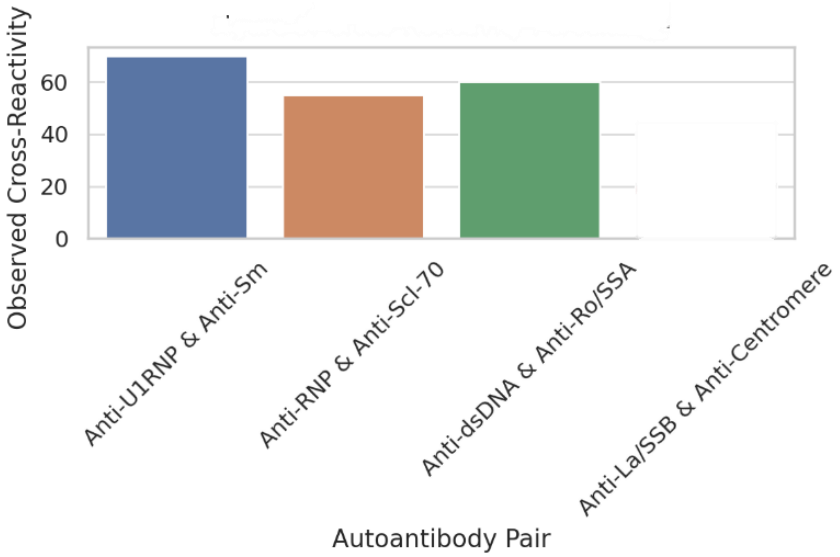

Figure 9: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.

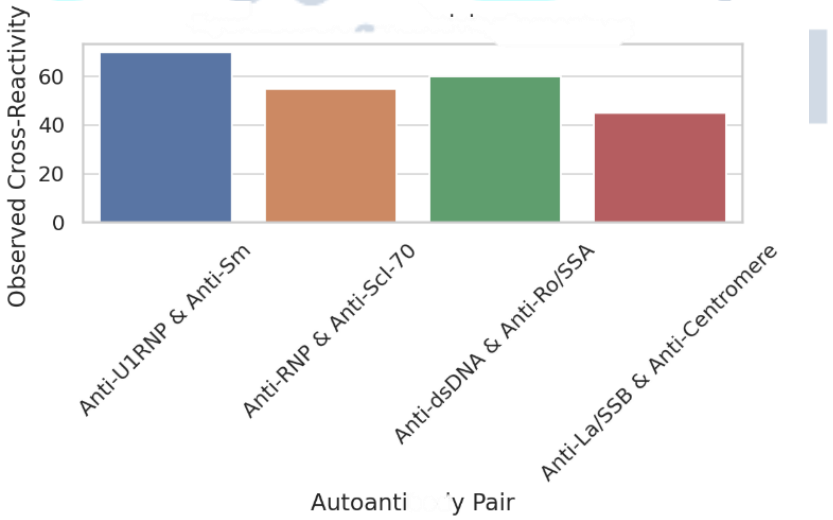

Figure 10: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.

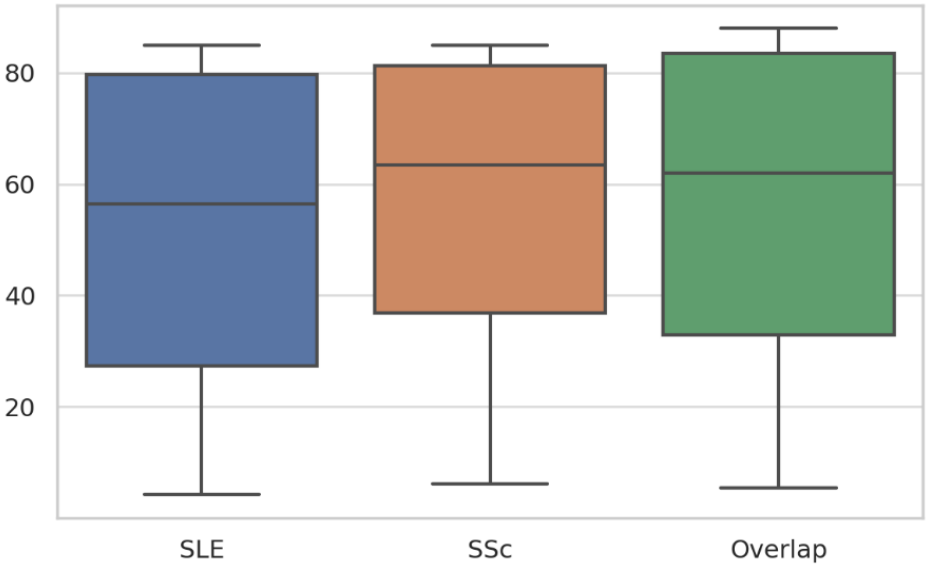

Figure 11: Autoantibody and Clinical Feature Analysis

This figure illustrates autoantibody frequencies, cross-reactivity, or clinical profile heatmaps in patients with SLE, SSc, and overlap syndromes.

4. DISCUSSION

When a patient displays signs of both systemic lupus erythematosus and systemic sclerosis, it is the presence of autoantibodies that helps detect the cause of the overlap syndrome. Having several autoantibodies implies they develop similarly and tend to respond to other molecules, leading to variations in symptoms (Vojdani et al., 2021). Similar autoantibody patterns were seen in patients with SLE, SSc and overlap syndrome and a large number of these patients had anti-RNP, anti-U1RNP and anti-Ro/SSA antibodies. Experts have identified that when you contract a viral infection, it can cause autoantibodies to respond to several self-antigens, leading to the different outcomes observed in autoimmune diseases (Cardoso et al., 2020). Many antigens share certain functions and structures that make it possible for autoantibodies to develop in the body (Munroe et al., 2021). Since both SLE and SSc have anti-Ro/SSA antibodies, it is clear that both types of immune disorders are likely related. It is possible for individuals with autoimmune diseases to experience even more serious health issues (Trier & Houen, 2023). If rheumatic diseases occur in a child or adolescent, antinuclear antibodies may be present in their bloodstream (Altay et al., 2021). In the years leading up to noticeable symptoms of arthritis, researchers commonly see autoantibodies, implying that these diseases are caused by inflammation and the immune system (Cruz et al., 2024). Some scientists think that in the presence of Epstein-Barr virus, antibodies can be generated that respond to certain proteins found in our body (Munroe et al., 2021).

Autoimmune diseases are caused when the immune system loses the ability to tolerate parts of the body, inflammation as a response to nucleic acids and immune complexes occurs and increased cytokine release, inflammation and tissue damage

result (Stergioti et al., 2022). The reason for a drop in tolerance may include hereditary traits, external aspects and some infections which then lead to active T and B cells that react to material in the body (Bhagavati, 2021). Since autoantibodies can be present in many of these diseases, it becomes crucial to perform a wide range of tests to find the autoantibodies that best characterize the specific illness. Having certain cross-reactive autoantibodies may influence the severity of a patient's disease and the results they achieve from regular treatments.

5. CONCLUSION

The study reveals that autoantibody cross-reactivity is vital in the body processes, diagnosing methods and complications found in these conditions. Examining autoantibody profiles in patients with lupus, scleroderma and related diseases allowed us to notice that many antibodies in SLE, SSc and overlap syndromes are the same, suggesting similar immunological processes occur in all of these diseases. Based on what we see in the data, it appears that, when molecules mimic those in the body and the immune system converges, tolerance can be broken and the immune system produces responses that cause disorders outside of those commonly accepted as diseases. Finding that anti-U1RNP connects with anti-Sm, anti-RNP with anti-Scl-70 and other anti-autoantibodies, points out that there may be a similarity among antigens in several autoimmune diseases. Moreover, people found to have both SLE and SSc frequently develop a range of issues that include lupus nephritis, arthritis, Raynaud's phenomenon and thickening of the skin. Because the disease is complex and assumes different forms, it must be managed carefully and treatment plans need to be created that address affected systems and different levels of immunity. The graph comparing age and positive test scores confirms that overlap syndromes should be seen as a special type of illness, unlike having two separate disorders. Based on our study, using broad autoantibody panels as part of routine diagnosis can greatly aid in early detection and prediction. It underlines that autoimmune overlap syndromes are best seen as overlapping immune processes which assists in giving patients the best possible diagnosis and therapy for their systemic autoimmune diseases.

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