Factors Associated With the Antinuclear Antibody Titer of Patients With Systemic Autoimmune Rheumatic Diseases After Treatment: A Retrospective Study

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Research Article

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Abstract

Background: Antinuclear antibodies (ANAs) are a serological hallmark of systemic autoimmune rheumatic diseases (SARDs); however, few studies have investigated their post-treatment levels.

Objective: The mechanism by which ANA titers are upregulated in SARDs remains unclear. We assessed factors associated with the ANA titer after treatment.

Methods: In this retrospective study we analyzed the clinical database of Zhongshan Hospital, Medical College of Xiamen. Demographic data and baseline and 12-month post-treatment ANA titers were collected. Bivariate and multivariate analyses were performed to determine the factors associated with the ANA titer.

Results: This study identified 31,923 patients who underwent ANA assay for SARDs screening, and a total of 1043 patients were included in the study. Approximately 16% of the patients showed a decrease in the serological ANA titer. Men were twice as likely to achieve a decrease in the serum ANA titer than women ($P = 0.055$), and younger patients (<20) were 3× more likely to experience such a decrease ($P = 0.005$) compared to older patients (≥60 years). A baseline ANA titer >1:10000 was associated with a significantly lower (47×) serum ANA titer compared with the baseline ANA titer at a dilution of 1:100 ($P < 0.001$).. Homogeneous ($P = 0.095$) and cytoplasmic speckled ($P = 0.158$) had over threefold greater decrease in the serum ANA titer compared with other patterns.

Conclusion: We found that a decrease in the serum ANA titer at 12 months after treatment for SARDs is associated with age, sex, ANA baseline titers, and ANA pattern.

Introduction

An autoimmune disease is a clinical syndrome that is caused by the activation of either T cells, B cells, or both in the absence of any other detectable cause. Although individually, autoimmune diseases are relatively rare, except for rheumatoid arthritis and autoimmune thyroiditis, collectively, they are known to affect nearly 3–5% of the world's population [1]. Autoimmune diseases can be classified as systemic or organ-specific. Systemic autoimmune rheumatic diseases (SARDs) are a family of more than 100 autoimmune diseases that are caused by the adaptive immune system and are characterized by the existence of antinuclear antibodies (ANAs) in the serum. The factors that influence ANA titer after treatment have not been well defined to date.

ANAs are a class of autoantibodies that have the ability to bind to and damage certain structures within the cell nuclei [2], leading to autoimmune disorders. Since the 1940s, the evaluation and diagnosis of SARD in clinical work has depended on the testing of ANA in the serum [3]. In the last few decades, the detection of ANAs has had an increasing influence for treating SARD patients in the clinical setting. Indeed, more laboratory support is needed for the clinician to obtain the most valuable possible diagnosis and analyze the clinical phenotype of individual patients [4, 5]. Serum ANA positivity is often a

determining factor in the clinician's diagnosis of SARD. Diseases such as scleroderma, systemic lupus erythematosus (SLE), Sjögren's syndrome, and rheumatoid arthritis, as well as other autoimmune conditions (e.g., hypothyroidism) and some chronic infections (e.g., bacterial endocarditis) are all linked to serum ANA positivity [6]. Not only do these antibodies affect disease pathogenesis, they also are key to the diagnosis and treatment of SARDs.

Among the various methods, the indirect immunofluorescence antinuclear antibody test (IIF-ANA) is the most commonly used for the detection of ANA and diagnosis of SARDs in daily clinical practice; the IIF-ANA is considered the "gold standard" for the diagnosis of SARDs. The ANA titer is directly proportional to the antibody concentration and shows a considerable range of values. A lower ANA titer is generally considered less significant than a higher titer with respect to SARDs, and it may even be seen in healthy individuals. Many studies attempted to determine the most favorable screening dilution of serum, and the International Consensus on ANA Patterns recommend that a 1:160 dilution be used for ANA testing for the diagnosis of SARD [7, 8]. A study reported that ANA testing should be performed only once and that positive results do not need to be repeated [9]. It is suggested that the ANA titer has no significance in rheumatoid arthritis and ankylosing spondylitis.

In the present study, we retrospectively analyzed the clinical database of Zhongshan Hospital, Medical College of Xiamen and performed bivariate and multivariate analyses to determine the factors associated with the ANA titer of SARDs patients who received recommended treatment.

Methods

Study population and ethics statement

This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, Medical College of Xiamen University, and was conducted in compliance with the national legislation and the Declaration of Helsinki guidelines. Written patient consent was obtained according to institutional guidelines. Data of subjects analyzed in the present study were extracted from the clinical database of Zhongshan Hospital, Medical College of Xiamen during the period between January 2012 and December 2019. Patients who were 12 years old or older, underwent reactive ANA tests for screening of SARDs were included. Patients were excluded from this study if they visited only once, were negative for ANA tests, had non-recommended therapy, were pregnant, without follow-up data for at least 1years after first ANA tests, without evaluated data and failed to treatment.

To assess the factors that are associated with the ANA titer after the patients were treated for SARDs, the patients were divided into two groups: a decrease group and a persistent group, based on whether the serological ANA titer decreased or persisted 12 months after therapy.

Serological tests

All the assays were performed using commercially available kits designed for clinical diagnosis according to the manufacturers' protocols.

ANA titers were determined by IIF-ANA using human epithelial type-2 (Hep-2) cells and commercially available ANA Hep-2 (Euroimmun Medizinische Labordiagnostika, Germany), as recommended by the manufacturer. Samples that tested positive for ANA at a dilution of 1:100 were tested again after being serially diluted to 1:320, 1:1000, 1:3200, 1:10000, and > 1:10000 until a negative result was obtained. The results were then determined with a fluorescence microscope and compared with negative and positive controls; the observer received standard training.

Treatment of SARD

Prednisone was found to be the most common medicine used to treat SARDs in patients, and for some patients it was administered in combination with chloroquine or chloroquine plus azathioprine. Methotrexate plus prednisone and chloroquine are used in fewer patients. Cyclophosphamide is rarely used. Patients who underwent plasmapheresis or plasma exchange were excluded. The dosage and length of treatment depended on the serum ANA indices as well as the clinical manifestations of the disease. The recommended therapeutic schedule for different diseases strictly follows the American College of Rheumatology (ACR)'s guidelines. Since the type of drug used, dosage, and route of administration affect the serum reaction, only patients who were treated with the above strategies were included in our study.

Study outcomes

The primary result was determined on the basis of change in the ANA titer 12 months after the treatment. A decrease in the serological ANA titer was defined as either a serum negative ANA test or a ≥ 2 dilution decrease in the ANA titer at 12 months after treatment. A persistent serological ANA titer status was defined as either no change in the ANA titer or a decrease or increase by ≤ 1 dilution from the baseline.

Data analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Bivariate analysis was utilized to analyze the factors associated with a decrease in serological ANA titer. Odds ratios (ORs) were estimated with 95% confidence intervals (CIs) from bivariate analysis, and factors with $P < 0.2$ were further identified in the multivariate analysis. Adjusted odds ratios (AORs) with 95% CIs were estimated from regression analysis. The results were considered statistically significant when the *P* value was < 0.05.

Results

Participant characteristics

In this study, we identified 31,923 patients in the Zhongshan Hospital database who were screened for SARDs by the ANA assay from January 2012 to December 2019. After excluding 30880 patients who

didn't meet criteria, 1043 patients were enrolled in our study ultimately (Fig. 1). The mean age was 42.9 years, and 83.9% were female. One year after therapy, most patients exhibited a constant serum ANA titer, but approximately 16% showed a decrease in the serum ANA titer (Table 1).

Factors associated with a decrease in the serum ANA titer

In our study, we compared the characteristics of 167 patients whose serum ANA titers with those of 876 patients whose serum ANA titers persisted at 12 months after treatment. Men were approximately twice as likely to achieve the decrease in the serum ANA titer than women (OR = 1.624, 95% CI: 0.99–2.667; P = 0.055) Compared with patients who were ≥ 60 years of age, those who were below 20 years of age were three times more likely to exhibit a decrease in the serum ANA titer (OR = 3.324, 95% CI: 1.428–7.326, P = 0.005). Moreover, patients who were 20–39 years of age had a slight probability of achieving a decrease in the serological ANA titer, which was the same as those who were 40–59 years of age. Patients with whose baseline serum ANA titer was higher easily achieved a decrease; in particular, a baseline ANA titer of > 1:10000 was associated with a 47-fold higher chance of a post-treatment decrease in serum ANA titer than a baseline ANA titer of 1:100 (OR = 47.339, 95% CI: 6.289–356.32, P < 0.001). Patients whose baseline ANA titers were 1:1000 (OR = 10.634, 95% CI: 4.754–23.79; P < 0.001), 1:3200 (OR = 9.93, 95% CI: 3.885–25.378; P < 0.001), and 1:10000 (OR = 22.342, 95% CI: 9.877–50.539; P < 0.001) had an increased likelihood of achieving a decrease in their 12-month post-treatment titer, but those with a baseline ANA titer of 1:320 had a decreased likelihood of achieving a decrease 12 months after treatment. The patterns of ANA expression were associated with increased odds of a decrease in the post-treatment serum ANA titer. Homogeneous (OR = 3.587, 95% CI: 0.803–16.028, P = 0.095) and cytoplasmic speckled (OR = 3.64, 95% CI: 0.605–21.902, P = 0.158) ANA patterns were more than three times more likely to achieve a decrease in the serum ANA titer compared with other ANA patterns; however, these differences were not significant. Those with speckled (OR = 2.192, 95% CI: 0.49–9.795, P = 0.304) and nucleolar (OR = 2.389, 95% CI: 0.387–14.764, P = 0.349) patterns were more than two times more likely to achieve a decrease in the post-treatment serum ANA titer compared to the other patterns. As shown by the P values, these differences were not statistically significant (Table 1).

Serological response based on baseline ANA titer

Based on the graph in Fig. 2, only 2.3% and 1.4% of participants whose baseline serum ANA titers were respectively 1:100 and 1:320, showed a decrease in the serum ANA titer. In contrast, 32.9% and 40.0% of patients whose baseline serum ANA titers were 1:10000 and > 1:10000 decreased 12 months after treatment. The results of the statistical analysis showed that patients with a higher baseline ANA titer were more likely to experience a subsequent decrease in the post-treatment ANA titers, especially among patients with a baseline ANA titer was ≥ 1:10000.

Prevalence of serological ANA positivity in SARDs

Figure 3 illustrates the distribution of these SARDs in a pie chart (Fig. 3). Among those in the decrease group, 58.7% (98/167) were diagnosed with SLE. The proportion of overlap syndrome and mixed connective tissue disease (MCTD) was approximately 9.6% (16/167; Fig. 3.a). Among those in the

persistent group, 50.3% (441/876) were diagnosed with SLE. Approximately 17.7% (155/876) and 15.6% (137/876) of the patients had Sjögren's syndrome (also called SICCA syndrome) and rheumatoid arthritis (RA), respectively (Fig. 3.b). We further investigated whether there were any differences in the patterns between the two groups. As shown in the pie charts (Fig. 3.c,d), there were no significant differences in the distribution of patterns between the decrease and persistent groups with SLE.

Multiple logistic regression analysis

Multiple logistic regression analysis was used to identify factors associated with this decrease in the serum ANA titer between the two groups. As shown in Table 2, interactions between age and ANA patterns with *P* values of < 0.001 were entered into the model. An age of < 20 years was linked to a greater than threefold increase in the likelihood of a decrease in the serum ANA titer than an age of ≥ 60 years and a higher AOR (AOR = 3.81, 95% CI: 1.738–8.379, *P* = 0.001). Compared with patients having a baseline serum ANA titer of 1:100, those with a baseline ANA titer of > 1:10000 (OR = 27.81, 95% CI: 3.997––193.497; *P* = 0.0.001), 1:10000 (OR = 20.293, 95% CI: 9.111–45.199; *P* < 0.001), 1:3200 (OR = 8.343, 95% CI: 3.318–20.976; *P* < 0.001) and 1:1000 (OR = 10.099, 95% CI: 4.563–22.351; *P* < 0.001) had a 27-, 20-, 8-, and 10-fold higher likelihood of achieving a 12-month post-treatment decrease, respectively (Table 2).

Serological response at different time points after therapy

In order to determine the time ANA titer achive a stable state, we analysis the rate of decrease of the ANA titer per month after therapy. As shown in Fig. 4, the number of patients whose serum ANA titer decreased with time showed an increasing trend. In our study, the serum ANA titer showed a percentage decrease of only 7.09% (57/1043) at 3 months and 9.4% (90/1043) at 6 months. The rate of decrease of the serum ANA titer slightly increased to 11.12% and 16%at 9 and 12 months after treatment, respectively.

Discussion

ANA testing has been crucial for the diagnosis of SARDs for the past 60 years. ANA titers and patterns are the most widely affected by SARDs, according to recommendations for assessing the clinical response to SARDs. Moreover, ANA may present years before obvious symptoms emerge, and in some cases, serological testing to detect ANA titers assays can provide valuable information for diagnosis and therapy. However, the ANA test cannot provide a prediction, diagnosis or activity assessment for certain autoimmune diseases [10]. Overall, the patient's needs for specific laboratory tests related to ANA-associated SARDs, such as SLE, systemic sclerosis (SSc), Sjögren's syndrome, MCTD or idiopathic inflammatory myopathies must also be considered [11]. Based on whether the ANA titers persisted (titers remaining the same as baseline levels) or decreased (by ≥ 2 dilution from the baseline or negative) at 12 months after recommended therapy, we divided patients into two groups: decrease and persistent. To date, this is the first evaluation of the factors influencing the serum ANA titer after recommended therapy for SARD. Additionally, the results of this study may guide clinicians in evaluating both the frequency of patient follow-up and analyzing the status of patients after treatment. Our study revealed that 84% of

1043 patients exhibited constant or persistent serum ANA titers and only 16% of patients exhibited a decrease in titer after 12 months of treatment. Higher ANA titers have a stronger correlation with SARDs and are more likely to be indicative of the autoantigen titer in follow-up testing [12–14].

What are the most important factors related to the serological decrease in the ANA titer in SARDs after recommended therapy? According to international recommendations, the ANA titer is determined mainly to diagnose SARDs and not to monitor disease activity [10]. In fact, the results of our bivariate and multivariate logistic analyses suggested that 16% of patients show a serological decrease in the ANA titer, with independent associations with sex, age, and baseline ANA titer.

For some patients with SARDs, the serological response differs over time after the recommended treatment has been administered. Therefore, the time point for the analysis is important in evaluating the serological response. In this study, we compared the rate of decrease in the serum ANA titer at different time points after treatment, and discovered that only 12% of patients with SARDs had a titer decrease at 12 months after treatment, with a slight increase of 1% at 18 months. These findings generally support that the ANA titer declines in some patients after therapy. In future studies, it would be appropriate to evaluate the serum ANA titer after 12 months of SARD treatment.

In our study, male patients were twice more likely to achieve a decrease in the serum ANA titer than female patients. While the sex ratios vary among the conditions presented herein, SARDs tends to mainly affect women, possibly owing to variances in susceptibility, hormonal influences, genetics, and exposure and response to environmental causes. Therefore, we concluded that differences in sex may influence the serological response after treatment. The specific mechanism underlying this association is unclear and further studies are needed to explore this in greater detail. Meanwhile, patients who were < 20 years of age were found to have a comparatively higher probability of achieving a titer decrease than patients in other age groups. Older populations tended to exhibit more degeneration of the immune system and immunosuppression, which would in turn affect the serological response to SARD treatment. Our findings suggest that the younger the patient’s age, the higher is the rate of decrease in the ANA titer. This finding is in agreement with results of Kurzinski et al., who proposed that ANA positivity can be used as a possible marker of relapse of disease activity with age[15, 16].

Our results point to a relationship between the baseline serum ANA titer and the serological response to recommended treatment for SARDs. The rate of decrease in the serum ANA titer after therapy was only 2.3% when the ANA titer was 1:100, but this rate reached 40% when the ANA titer was > 1:10000. After treatment, the rate of decrease in the serum ANA titer increased with an increase in the baseline serum ANA titer. Conversely, the rate of serum ANA titer persistence decreased with an increase in the baseline serum ANA titer. Patients with SARDs who do not achieve a decrease in ANA titer and continue to show a positive reaction remain a clinical challenge. ANA IgG antibodies are a dominant feature of SARDs. Our previous study showed that high-affinity ANAs (HA) may be a new biomarker for diagnosing SLE and identifying SLE activity.[17] High-affinity antibodies mediate a variety of biological functions more effectively than low-affinity antibodies[18]. We speculated that HA may be the main cause of the

persistence in the serum ANA titer. A previous study showed that SLE is typified by increased ANA + IgG plasmablasts/plasma cells (PCs) through aberrant IgG PC differentiation rather than an antigen-specific tolerance defect[19]. In other words, the reason for the decrease in the serum ANA titer may be that some media preferentially target the germinal center (GC) PC differentiation pathway and others target the extrafollicular pathway[20]. Serum ANA positivity of the IgG isotype (IgG-ANAs) suggests a diagnostic index for patients with SLE and other SARDs, and these antibodies play an important role in disease pathogenesis[19]. After recommended therapy, nuclear or cytoplasmic antigens clear, and autoantibodies gradually disappear, with reduction in aberrant IgG PC differentiation. Comparatively, IgM-ANAs are found in healthy populations and help clear cellular debris without causing inflammation. IgM-ANAs function in protecting against autoimmunity disorders because they inhibit proinflammatory responses induced by IgG-ANAs[21]. However, the exact mechanism of this is unclear and needs to be studied in more detail.

Determining the HEp-2 IIFA patterns in the context of disease manifestations is a crucial tool in the clinical diagnosis of patients suspected of having SARDs. Our findings indicated that 58.68% (98/167) of patients were diagnosed with SLE in a decreasing titer status and as much as 50.34% (441/876) with SLE with a persistent serum ANA titer. Nonetheless, the rate of homogeneity or speckling patterns did not differ between the two statuses. In general, the results of the ANA pattern in our study were strongly associated with SLE disease.

Our study has several limitations. Due to its retrospective design, information can only be collected from medical records, and this information is not precise. It is difficult to entirely exclude treatment relapse among our patients, which can lead to prolonged seroactivity. Finally, the patients who were deemed appropriate for the analysis were patients whose ANA tests were documented during the research period; thus, there is the possibility of selection bias. Whether the exclusion of patients who did not have documented ANA tests affected the outcome of our study is unknown. In addition, the IIF-ANA test is limited by its relatively low standardization and automation, subjective evaluation, intra- and interlaboratory variability, and the need for expert training to perform the test.

To date, studies on the serum ANA titer in response to treatment for SARDs are rare. Our report analyzes and discusses the factors associated with two statuses in ANA-positive patients after treatment. Although ANA testing is generally not considered to be an indicator of disease activity in SARD, we found factors that were associated with the serum ANA titer after therapy, indicating that ANA testing has other implications that are yet to be described. We hope that the finding of this study provides useful insights to clinicians and public health workers to help them distinguish the statuses of different patients with SARDs, providing an explanation to the patients about their disease state, and weighing expected outcomes after therapy.

Conclusion

A persistent serum ANA titer is common in clinical work, as seen in previous studies. In our study, we found that the 12-month post-treatment decrease in serum ANA titer is associated with age, sex, baseline

ANA titer, and ANA pattern. Further research into the factors affecting the decrease in the serum ANA titer after treatment and its role in SARDs is warranted.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, Medical College Xiamen University, and performed in compliance with national legislation and the Declaration of Helsinki guidelines.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All the data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing financial interests.

Authors' contributions

Y-LZ, YX, and Y-QL conceived and designed the experiments. YZ and J-JW performed the experiments. Y-LZ and YX analyzed the data. Y-QL contributed reagents/materials/analysis tools. YX and Y-LZ wrote the paper. Y-LZ critically revised the manuscript for intellectual content. All the authors have read and approved of the final manuscript.

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Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

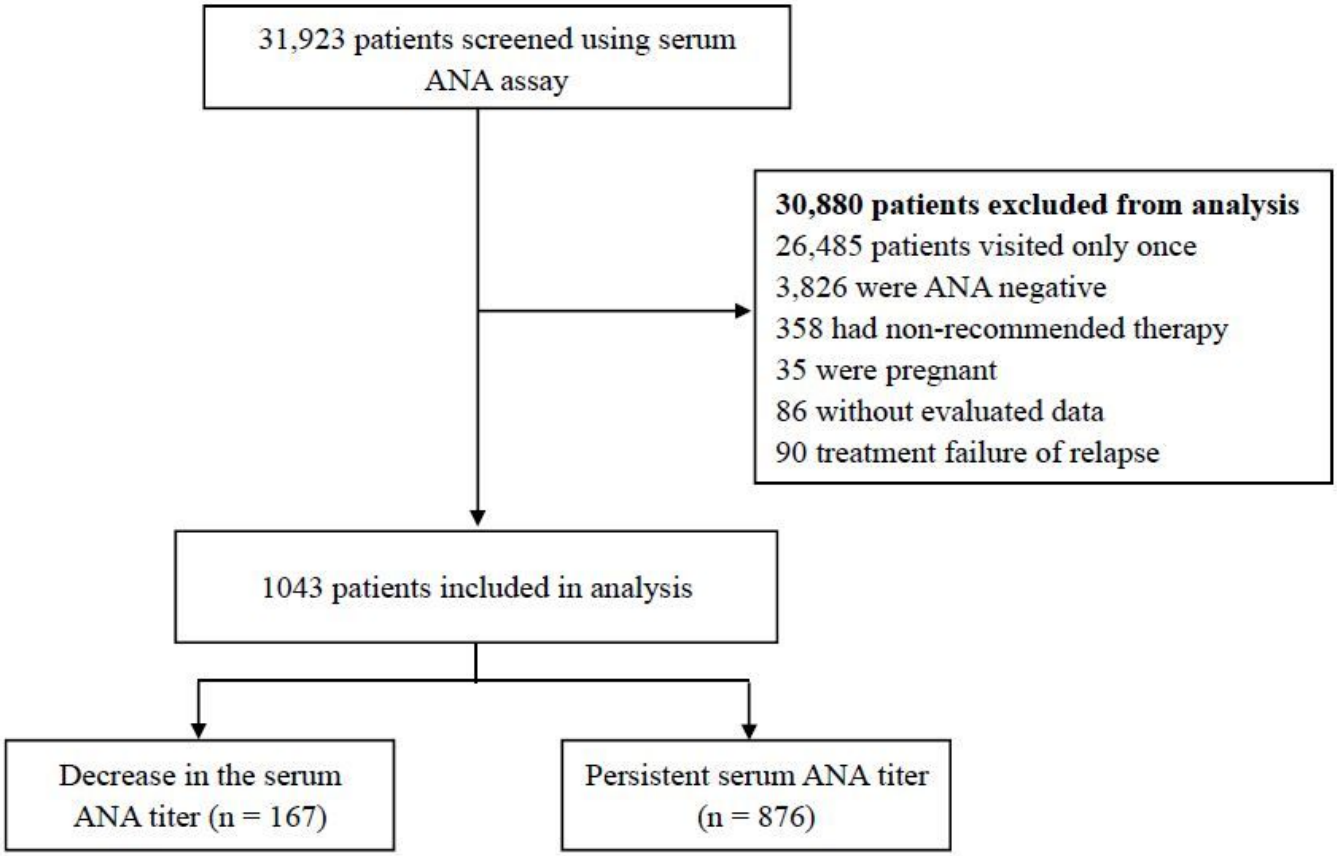

Figure 1

After excluding 30880 patients who didn't meet criteria, 1043 patients were enrolled in our study ultimately (Figure 1).

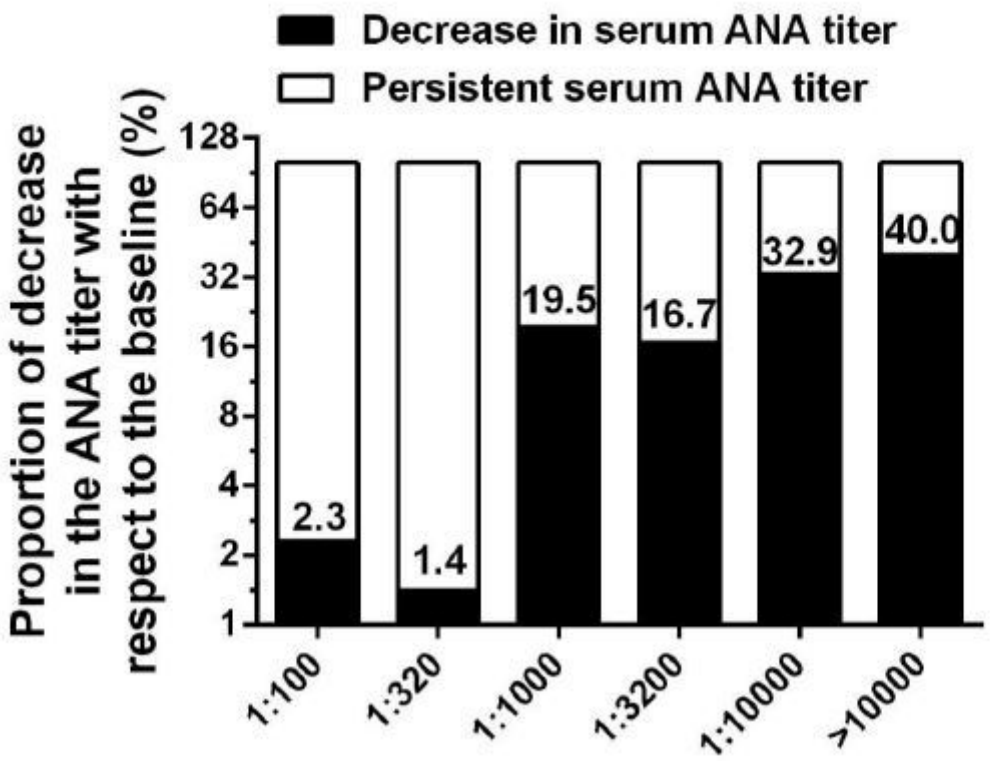

Figure 2

In Fig. 2, only 2.3% and 1.4% of participants whose baseline serum ANA titers were respectively 1:100 and 1:320, showed a decrease in the serum ANA titer.

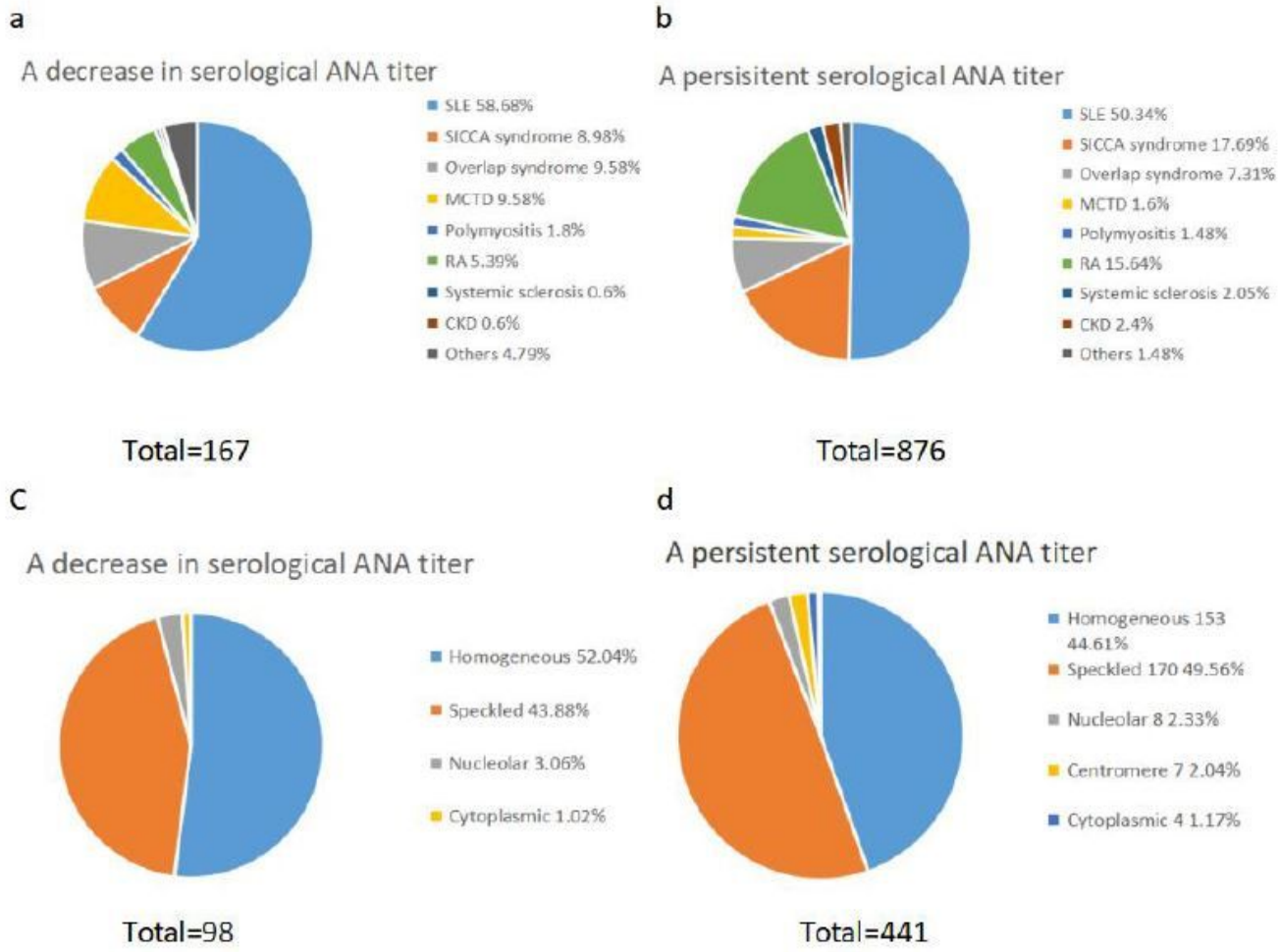

Figure 3

Figure 3 illustrates the distribution of these SARDs in a pie chart (Figure 3).

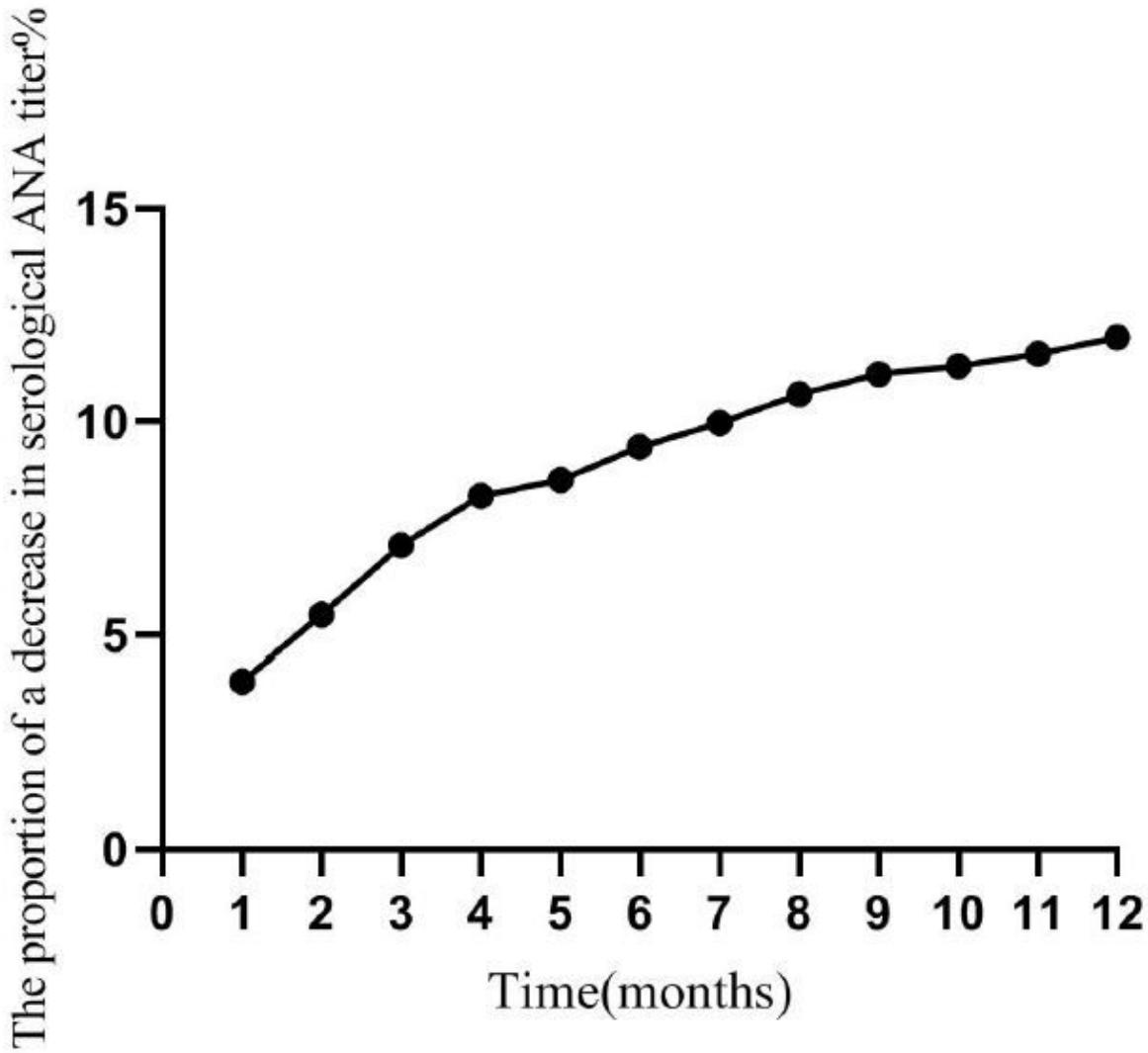

Figure 4

As shown in Fig. 4, the number of patients whose serum ANA titer decreased with time showed an increasing trend. In our study, the serum ANA titer showed a percentage decrease of only 7.09% (57/1043) at 3 months and 9.4% (90/1043) at 6 months.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.pdf
- table2.pdf