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Original Article

The Effect of Estradiol and Testosterone Levels Alone or in Combination with Their Receptors in Predicting the Severity of Systemic Lupus Erythematosus: A Cohort Study

Samaneh Abdolahpour[1], PhD; Nafiseh Abdolahi[1], MD; Mehrdad Aghaei[1], MD; Hossein Azadeh[2], MD; Touraj Farazmandfar[3], PhD

[1]Golestan Rheumatology Research Center, Golestan University of Medical Sciences, Gorgan, Iran;
[2]Department of Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran;
[3]Medical Cellular and Molecular Research Center, Golestan University of Medical Sciences, Gorgan, Iran

Correspondence:
Touraj Farazmandfar, PhD;
Medical Cellular and Molecular Research Center, Golestan University of Medical Sciences, Falsafi complex, Shastkola Road, Postal code: 49341-74611, Gorgan, Iran
Tel: +98 17 32451563
Email: dr.farazmandfar@goums.ac.ir
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Abstract

Background: Developing a practical method to predict active systemic lupus erythematosus (SLE) in patients with inactive/mild status at the onset of the disease could lead to appropriate treatment that ultimately prevents future relapses. The development of SLE is influenced by steroid hormones and probably the receptors of these hormones. Therefore, we aimed to investigate the predictive effect of the levels of estradiol and testosterone hormones and their receptors on the severity of SLE disease.

Methods: Serum samples were taken from 59 female patients with inactive SLE in Golestan province in northern Iran. The concentration of estradiol (E2) and testosterone (T) hormones and their receptors, estrogen receptors (ER) and androgen receptors (AR), was measured at the beginning of the study after sampling. After a one-year follow-up (2021 to 2022), the patients were divided into active and inactive SLE groups based on the clinical criteria of the SLE activity index. *T* test and Mann-Whitney U-test were used to analyze the difference of variables. The correlation was analyzed using Pearson and Spearman tests. Discriminative power was measured, and a cut-off point was suggested.

Results: There was a significant difference in the average E2+ER/T+AR ratio between active and inactive SLE groups ($P<0.001$). It was also found that this ratio has a significant correlation with the severity of the disease ($r=0.546$, $P<0.001$).

Conclusion: Despite the normal concentration of each steroid hormone and its receptors, the E2+ER/T+AR ratio may be a good indicator of the development of active SLE.

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Keywords ● Lupus erythematosus, systemic ● Gonadal steroid hormones ● Estrogen receptor alpha ● Receptors, androgen

What's Known

- Systemic lupus erythematosus is highly gender-dependent, with a prevalence nine times higher in women than in men.
- Steroid hormones play an important role in B cells' maturation, differentiation, and activation, potentially stimulating the immune system.

What's New

- The ratio of estradiol+estrogen receptor/testosterone androgen receptor significantly correlates with the severity of the systemic lupus erythematosus.
- This ratio may be a good indicator for predicting active systemic lupus erythematosus development.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammation and tissue damage in affected organs. This disease is highly gender-dependent, with a prevalence nine times higher in women than in men.[1, 2] Previous studies have shown that estrogen plays an important

role in the maturation, differentiation, and activation of B cells, potentially stimulating the immune system.[3, 4] Administration of estradiol (E2), a highly active metabolite of estrogen, exacerbates disease symptoms in women, including increased Anti-double stranded DNA (dsDNA), deposition of immune complexes in the glomerulus, and proliferation and activation of reactive B cells.[5] Estradiol activates estrogen receptors (ER) and leads to their translocation to the nucleus and binding to estrogen response elements in the promoter of the corresponding genes. ER consists of two types: alpha (ERα) and beta (ERβ). Although both types of ER receptors are present in most immune cells, the ERα type is predominantly expressed.[6-9] The role of ERα in the induction of interferon-gamma, reduction of immune tolerance, and production of pathogenic antibodies has been confirmed.[10] Recent studies using selective ER agonists in a mouse model of lupus and humans have shown that ERα activation promotes SLE disease progression.[11, 12]

Reports show that androgens, especially testosterone (T), have a protective role in SLE patients, so the difference in the concentration of this hormone between the two genders may explain the increased incidence of the disease in women. Klinefelter syndrome (XXY syndrome) has been reported to be associated with a higher prevalence of SLE among males.[13] Testosterone binds to androgen receptors (AR) expressed in most immune cells, is transferred to the nucleus as a ligand-receptor complex, and regulates transcription by binding to androgen response sequences on DNA.[14] Testosterone promotes the proliferation of suppressor T cells while inhibiting the synthesis of pro-inflammatory mediators such as Tumor Necrosis Factor-alpha and interleukin 10.[15] Hence, administering danazol (a synthetic androgen) in women with SLE reduces total plasma Immunoglobulin G levels and anti-dsDNA antibodies.[16]

To date, there is no reliable laboratory method for predicting the progress of the disease, which may delay definitive diagnosis and timely treatment for several years. Therefore, performing a particular test to predict the recurrence of the disease at the beginning of the patient's visit can lead to prescribing the appropriate type and dosage of the drug and finally prevent the recurrence of the disease in the future. The relationship between estradiol and testosterone and the progression of SLE has not been investigated through the changes of their receptors in immune cells. Defects in these receptors may impair the hormonal response, even with normal hormonal levels. Moreover, the serum concentration of these receptors may reflect their abundance in immune cells. Thus, the combined measurement of hormones and their receptors may better indicate their function. Previous studies have shown that estradiol worsens SLE while testosterone ameliorates it.[6-9, 13-15] Hence, the ratio of estradiol and its receptor to testosterone and its receptor may predict the disease severity. For the first time, we measured the concentration of these hormones and their receptors in the serum of patients with inactive/mild SLE. We developed a functional formula to forecast the onset of active SLE.

Patients and Methods

Sample Collection

This study was conducted in 2021-2022 at Golestan University of Medical Sciences in Golestan province in northern Iran. Serum samples were collected from 59 women aged 25 to 45 years with inactive SLE based on Systemic Lupus International Collaborating Clinics (SLICC) Criteria (2012),[17] and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[18] of less than five, before drug treatment. The severity of the disease was recorded by a rheumatologist during clinical and paraclinical examinations based on the SLEDAI, with inactive SLE defined as SLEDAI=0, mild SLE as SLEDAI=1-5, and active SLE as SLEDAI>5. Exclusion criteria included other vascular collagen diseases, the use of birth control pills or any type of steroid hormone, pregnancy, infertility, and menstrual irregularities. At the end of the follow-up, patients with very different treatment profiles were excluded from further analysis. Sampling was performed on days 0 to 8 of the menstrual cycle to avoid recording severe hormone changes. All laboratory tests without statistical analysis were performed after sampling at the beginning of the project for all samples. They were followed for one year to determine which patients would develop active lupus in the future. Then, they were divided into two groups: inactive and mild lupus (SLEDAI≤5) (n=29) and active lupus (SLEDAI>5) (n=30). The study design is summarized and schematically shown in figure 1. The study was conducted in accordance with the Declaration of Helsinki and the Ethics Committee of Golestan University of Medical Science (IR.GOUMS.REC.1400.321). All patients gave written informed consent for participation in the study.

Enzyme-Linked Immunosorbent Assay (ELISA)

The levels of estradiol and testosterone

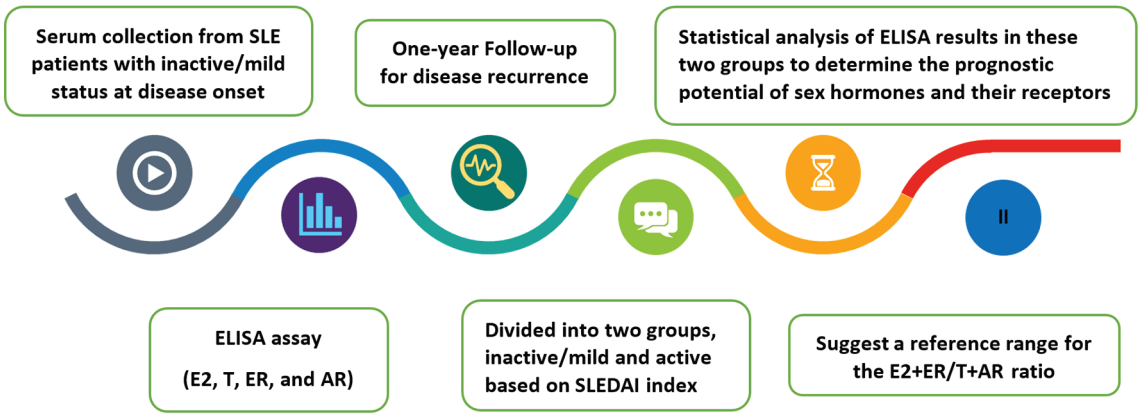

Figure 1: The schematic summary of the study design shows the time course of the study. E2: Estradiol; T: Testosterone; ER: Estrogen receptor; AR: Androgen receptor; SLEDAI: Systemic Lupus Erythematosus Activity Index

and their receptors in the serum of patients were measured by using estradiol ELISA Kit (Arborassays, Ann Arbor, USA), testosterone ELISA Kit (MyBioSource, San Diego, USA), Estrogen Receptor Alpha ELISA Kit (MyBioSource, San Diego, USA), and Androgen Receptor ELISA Kit (MyBioSource, San Diego, USA). Estradiol and testosterone hormones were measured in their free forms. The receptors were also measured in total, indicating their quantity in cells under the effect of hormones. According to the kits' protocols, 100 µL of serum and standards were added to each well on a 96-well plate covered with anti-hormone or anti-receptor, incubated for 90 min at room temperature, and then washed. Next, 100 µL of the detection antibody solution was added to each well, incubated for 30 min at room temperature, and then washed. Subsequently, 200 µL of substrate solution was added to each well with a 30 min incubation at room temperature. Finally, 50 µL of stop solution was added. The optical density of the wells was immediately measured by a microplate reader (Awareness Technology, Palm City, USA) at 450 nm. The levels of hormones and their receptors were calculated based on a standard curve (Supplementary).

Statistical Analysis

Data were analyzed using GraphPad software (GraphPad, La Jolla, USA). All tests were performed in triplicate, and variables were recorded as the mean±SD. The mean values of each group were expressed as mean±SEM. The normality of the variables was checked using the Shapiro-Wilk test. *T* test was used to analyze the difference of variables with normal distribution, and the Mann-Whitney U-test was used to analyze the difference of variables with non-normal distribution. Correlation analysis was performed using Pearson and Spearman tests. Discriminative power was measured by the area under the receiver operating characteristic (ROC) curve, and cut-off points were suggested utilizing the index of union (IU) method.[19] A P value less than 0.05 was considered significant.

Results

Although there was no significant difference between the mean estradiol and testosterone levels in the active and inactive/mild SLE groups, the mean estradiol-to-testosterone ratio was significantly higher in the active group compared to the inactive/mild group (P=0.025) (figure 2A). There was no significant difference in the mean level of estrogen receptors between the active and inactive/mild SLE groups. However, the mean level of androgen receptors in the active group was significantly lower than in the inactive/mild group (P=0.001). The mean estrogen receptor/androgen receptor ratio in the active group was also significantly higher than in the inactive/mild group (P=0.001) (figure 2B).

In this study, the effects of the combination of hormones and their receptors and the ratio of these two compounds were evaluated as an indicator to predict the disease progression to active SLE. The results showed that the mean combination of estradiol and estrogen receptors in the active group was significantly higher than in the inactive/mild group (P=0.016). In comparison, the mean combination of testosterone and androgen receptors in the active group was significantly lower than in the inactive/mild group (P<0.001). The mean of the E2+ER/T+AR ratio was also significantly higher in the active group than in the inactive/mild group (P<0.001) (figure 2C).

To confirm the results of the previous step, the relationship between estradiol, testosterone, and their receptors (measured at baseline) with the SLE disease severity index after follow-up was also investigated in this study.

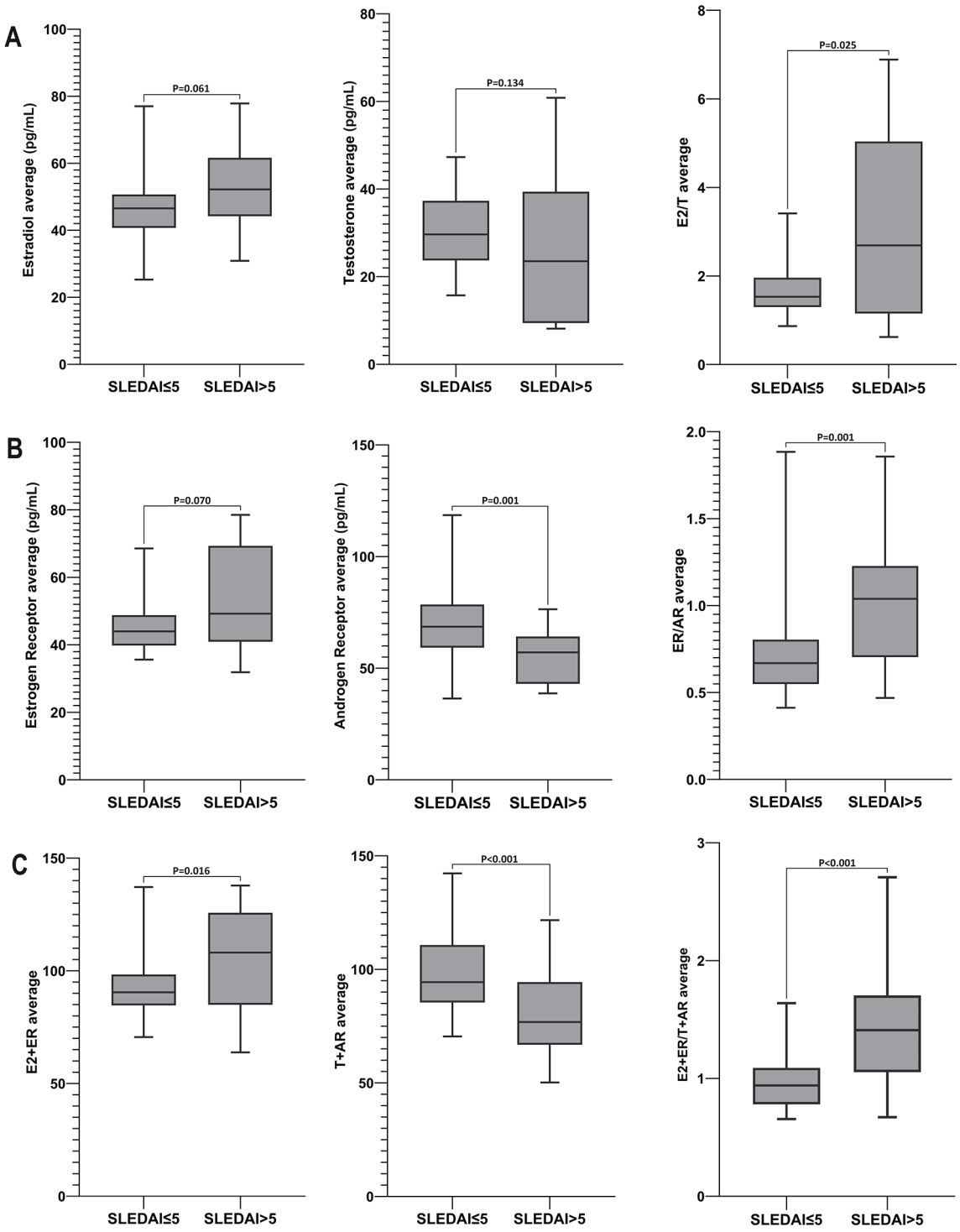

Figure 2: Hormones, receptors, and their ratios were measured at the beginning of the study and compared after one year of follow-up between active and inactive/mild SLE groups. A) Comparison of the mean E2 and T hormones and their ratio in active and inactive/mild SLE groups. B) Comparison of the mean ER and AR and their ratio in active and inactive/mild SLE groups. C) Comparison of mean E2+ER and T+AR complexes and their ratio in active and inactive/mild SLE groups. SLEDAI: Systemic Lupus Erythematosus Activity Index; E2: Estradiol; T: Testosterone; ER: Estrogen receptor; AR: Androgen receptor

As figure 3A shows, estradiol has a significantly weak positive correlation with the SLE disease severity index (r=0.348, P=0.006), while testosterone has a significantly weak negative correlation with the disease severity index (r=-0.374, P=0.003). There is also a significant weak positive correlation between the ratio of estradiol to testosterone and the SLE disease severity index (r=0.473, P<0.001). The estrogen receptor had a significant weak positive correlation with the SLE disease severity index (r=0.270, P=0.036), while the androgen receptor had a significant weak negative correlation with the disease severity index (r=-0.384, P=0.002).

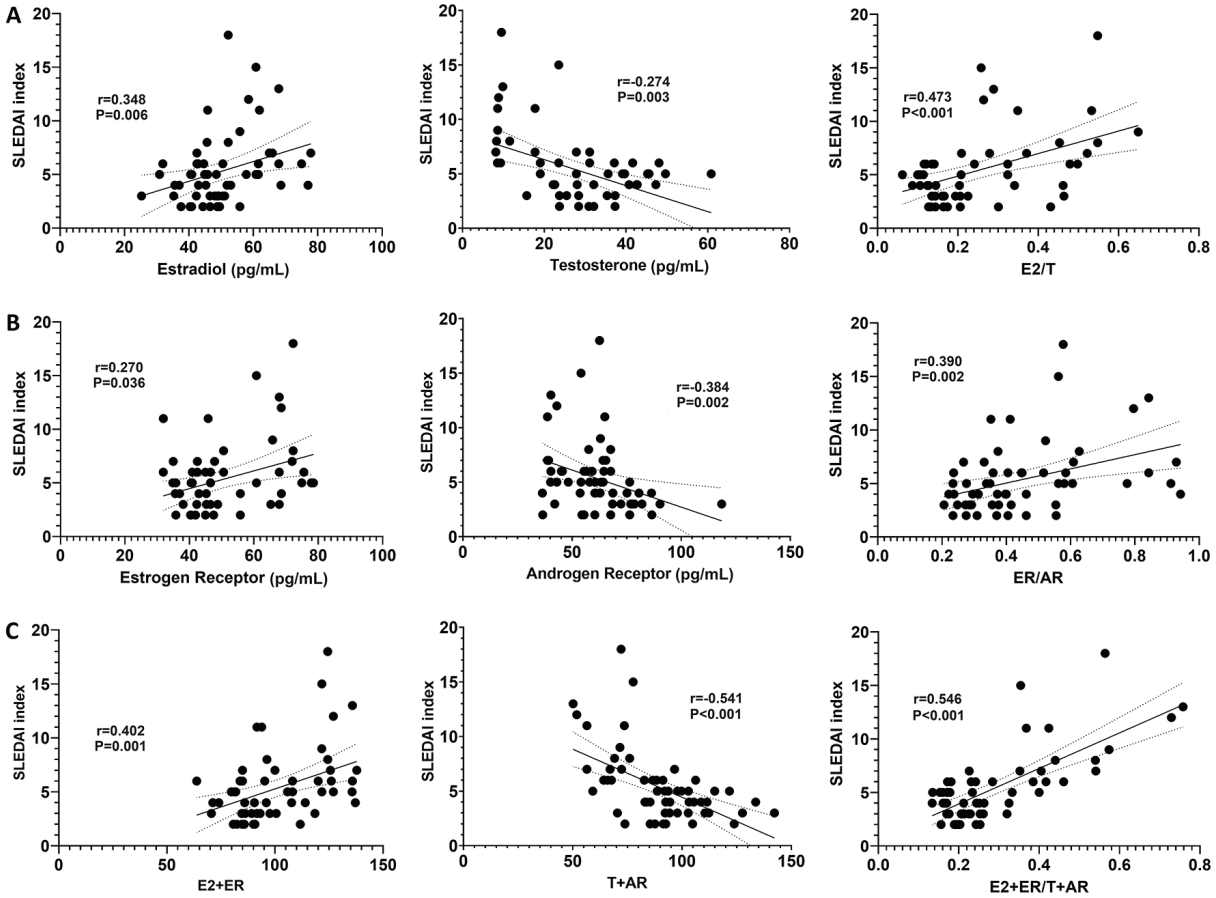

Figure 3: Hormones, receptors, and their ratios were measured at the beginning of the study; and after one year of follow-up, their correlation with the disease severity index was investigated. A) Correlation of E2 and T hormones and their ratios with disease severity index. B) Correlation of ER and AR hormones and their ratios with disease severity index. C) Correlation of E2+ER and T+AR complexes and their ratio with disease severity index. SLEDAI: Systemic Lupus Erythematosus Activity Index; E2: Estradiol; T: Testosterone; ER: Estrogen receptor; AR: Androgen receptor

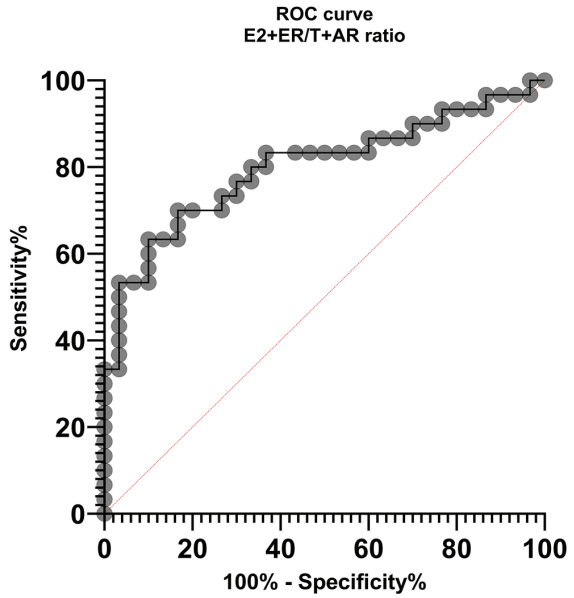

Figure 4: The discriminatory power of the cut-off point was analyzed by the receiver operating characteristic (ROC) curve. A value of 1.17 with a sensitivity of 70% and a specificity of 83.33% (P<0.001) has been suggested as a threshold value for susceptibility to active SLE based on the index of union (IU) method. E2: Estradiol; T: Testosterone; ER: Estrogen receptor; AR: Androgen receptor

There was also a significant weak positive correlation between the estrogen receptor/androgen receptor ratio and the disease severity index (r=0.390, P=0.002) (figure 3B). According to the correlation pattern of hormones and their receptors, the results of figure 3C showed that the combination of estradiol and estrogen receptors has a significant weak positive correlation with the SLE disease severity index (r=0.402, P=0.001). In contrast, the combination of testosterone and androgen receptors has a significant moderate negative correlation with the disease severity index (r=-0.541, P<0.001). There was also a significant moderate positive correlation between the E2+ER/T+AR ratio and the disease severity index (r=0.546, P<0.001).

This study also calculated and suggested a cut-off point for the E2+ER/T+AR ratio. This point for this ratio, according to the IU method, was reported as 1.17 with a sensitivity of 70% and a specificity of 83.33% (P<0.001) (figure 4).

Discussion

This study showed that measuring the ratio of

the cumulative effect of steroid hormones and their receptors in the inactive/mild state of SLE may be an indicator to predict the development of the active state of the disease in the future. One of the major problems in treating SLE is the lack of predictability of disease progression to the active stage. Predicting the progression of the disease may lead to early administration of drugs that inhibit the progression of the disease in the appropriate type and dosage. Therefore, finding a prognostic factor to improve the treatment process would be very promising. For practical use of these predictors in medical centers related to the diagnosis and treatment of SLE, it is necessary that any user can easily measure this factor with a simple and inexpensive device. One of the best predictors may be the readily available substances in the blood. Given the known effect of steroid hormones on modulating the immune system, they may be one of the best options for predicting the progression of SLE. These hormones can be easily measured by a simple ELISA device by any medical staff at any level. The effects of estradiol and testosterone on the development and control of autoimmune diseases have been demonstrated.[20-23] Considering the function of immune cells under the influence of steroid hormones,[24, 25] it can be concluded that the concentration of their receptors may also play a role in the intensity of the effects of these hormones. In addition to the ligand-dependent impacts, ligand-independent effects of these receptors can also exacerbate autoimmune diseases.[26, 27] The strength of this study is perhaps the design of the study with its own grouping, which has led to the creation of a specific model that can be used to predict the severity of diseases. In this study, unlike previous studies, the measurement of hormones alone was not related to the development of SLE disease.[28, 29] However, due to the specific design of this study on the combination of hormones with receptors, the limitation of samples for women, and the absence of studies with similar grouping, it is impossible to compare our results with other studies. One of the challenging limitations of this study may have been the effect of treatment on disease severity during follow-up. Therefore, we tried to exclude patients with very different treatments at the end of the study. In addition, the suggested cut-off point based on discrimination power had moderate accuracy, which could be due to the small volume of samples. Confirming this cut-off point requires a larger sample size in future studies.

Conclusion

This study suggests that the cumulative effect of steroid hormones and their receptors may be considered as an indicator for predicting the severity of SLE. Considering the ease of measuring these factors in the blood, the presented formula can be a simple and low-cost method to predict the progress of the disease. Furthermore, this information may provide a deeper understanding of the pathophysiology of lupus in women, which will be very useful in designing an effective treatment. It is suggested to conduct a similar study with larger sample size and more related variables in the future to increase the strength and accuracy of the prognostic value of steroid hormones in predicting the severity of SLE.

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Authors' Contribution

S.A: Data gathering, data analysis, and drafting; N.A: Data gathering, study design, and critical revision; M.A: Data gathering, data analysis, and critical revision; H.A: Data gathering, data analysis, and critical revision; T.F: Study design, data analysis, and critical revision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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