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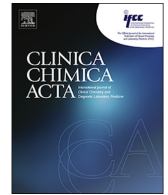

Serum leucine-rich α2-glycoprotein is elevated in patients with systemic lupus erythematosus and correlates with disease activity

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ABSTRACT

Background: We evaluated whether serum leucine-rich α2-glycoprotein (LRG) is associated with disease activity in patients with systemic lupus erythematosus (SLE).
Methods: We measured serum LRG in 194 SLE patients. SLE disease activity index-2000 (SLEDAI-2 K) was used to assess SLE activity, and patients with SLEDAI-2 K ≥ 5 were defined as having active SLE. Correlation between serum LRG, SLEDAI-2 K, and laboratory variables was estimated by Pearson's correlation analysis. The optimal serum LRG cut-off value for predicting active SLE was calculated using receiver operator characteristic (ROC) curve, and multivariable logistic regression was used to determine the odds ratio (OR) of laboratory variables.
Results: In total, 74 (38.1%) and 120 (61.9%) patients were classified as active and inactive SLE, respectively. Serum LRG was higher in patients with active SLE than in inactive SLE and healthy controls (26.6 vs. 14.4 vs. 1.2 ng/ml, $p < .001$). Serum LRG significantly correlated with SLEDAI-2 K ($r = 0.340$, $p < .001$) and laboratory variables. ROC analysis revealed that optimal serum LRG cut-off value for active SLE was > 45.7 ng/ml. In multivariable logistic regression analysis, serum LRG > 45.7 ng/ml (OR 4.089, 95% confidence interval 1.351, 12.376, $p = .013$) was an independent predictor of active SLE.
Conclusions: Serum LRG might be a biomarker for estimating SLE disease activity.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can provoke various systemic inflammatory conditions, including encephalitis, pneumonitis, and glomerulonephritis, through a dysregulation of the immune response [1]. While remarkable advancements have been made over the past decades to understand the underlying mechanism of this disease, SLE still remains a clinical challenge, considering the wide variation in the clinical manifestation of this disease and its fluctuating clinical course [2,3]. Furthermore, in the treatment of SLE, a proper and timely approach based on disease activity, can improve prognosis. Therefore, accurately estimating SLE activity may be as important as diagnosing the condition. Currently, the SLE disease activity index-2000 (SLEDAI-2 K) is the most widely used tool to estimate disease activity [4]. The SLEDAI-2 K consists of 24 items, including anti-dsDNA and complements. However, completion of the SLEDAI-2 K form can take several minutes and may be associated with inter-observer variability or bias [5]. Accordingly, in the clinical settings, the needs to discover a biomarker that could reflect SLE activity has been continuously raised [6].

Leucine-rich α2-glycoprotein (LRG), first isolated in 1977, is a plasma glycoprotein containing repetitive leucine-rich sequences [7,8]. Although the role of LRG in the inflammatory process is unclear, it is known that the LRG protein is secreted during the acute phase of inflammation, in response to inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and the tumour necrosis factor (TNF)-α [9]. In this context,

Abbreviations: C3, complement 3; C4, complement 4; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; LRG, leucine-rich α2-glycoprotein; OR, odds ratio; ROC, receiver operator characteristic; RR, relative risk; SLE, systemic lupus erythematosus; SLEDAI-2 K, SLE disease activity index-2000; Th, T helper; TNF, tumour necrosis factor; WBC, white blood cell

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serum LRG was reported to be elevated in various autoimmune diseases with levels correlating to disease activity in rheumatoid arthritis, adult-onset Still's disease, inflammatory bowel diseases, and psoriasis [10–13]. Because IL-1β, IL-6, and TNF-α are important cytokines in the pathogenesis of SLE, serum LRG may be elevated in SLE and correlate with its activity. However, to date, there is no report regarding serum LRG in patients with SLE. Therefore, our aim in this study was to investigate the clinical significance of serum LRG in SLE.

2. Materials and methods

2.1. Patient selection

We reviewed the medical records of 194 patients who had been diagnosed with SLE at the Division of Rheumatology, Yonsei University College of Medicine, Severance Hospital, between March 2015 and September 2016, and for whom blood samples were available for analysis. The following patients were included: 1) those who fulfilled the 1997 revised American College of Rheumatology classification criteria for SLE [14]; 2) who had no other medical conditions, such as malignancy, infectious diseases, and autoimmune diseases other than SLE; and 3) whose calculated SLEDAI-2 K were available in the medical records on the same day of serum storage. For comparison, serum sample of age- and sex-matched healthy controls (n = 39) were collected, after obtaining informed consent at the Severance Hospital Health Center (4–2017-0761). This study was approved by the Institutional Review Board of Severance Hospital and conducted in accordance with the principles set forth in the Declaration of Helsinki.

2.2. Clinical and laboratory data

We collected demographic data including age, gender, and disease duration. Disease duration was defined as the period from SLE diagnosis to the day of serum storage. We used the SLEDAI-2 K as a measure of SLE activity [4], with a cut-off SLEDAI-2 K value ≥5 used to define an active SLE state [15]. Clinical manifestations of SLE included the presence of a skin rash, photosensitivity, oral ulcers, arthritis, serositis, and nephritis, as well as neurological, haematological and immunological disorders, as per the 1997 revised American College of Rheumatology classification criteria for SLE [14]. The following laboratory variables were included in the analysis: anti-dsDNA level, complement 3 (C3) level, complement 4 (C4) level, white blood cell (WBC) count, lymphocyte count, platelet count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. In addition, we reviewed the medications being used at the time of serum storage using the Korean Drug Utilisation Review system.

2.3. Calculation of serum LRG level by ELISA

Serum LRG level was measured from stored serum samples in both SLE patients and the control group. ELISA kits for LRG measurement were purchased from IBL (Gunma, Japan), with levels determined according to the manufacturer's instructions. Briefly, for each serum samples, 100 μl of the serum was added to each well and the plate was covered using a plate sealer and incubated overnight at 4 °C. Each well was then washed seven times, using a washing buffer, and 100 μl of labelled antibody solution was subsequently added to each well. Again, the plate was covered with the plate sealer and incubated for 30 min at 37 °C. The plate was then washed nine times, using a washing buffer. Subsequently, 100 μl of 3, 3′, 5, 5′ - tetramethylbenzidine substrate solution was added to each well, and the plate was incubated for 30 min at room temperature, in the dark. Following this final period of incubation, 100 μl of a stop solution (1 N Sulfuric acid) was added to each well and the OD value of each well was measured at 450 nm.

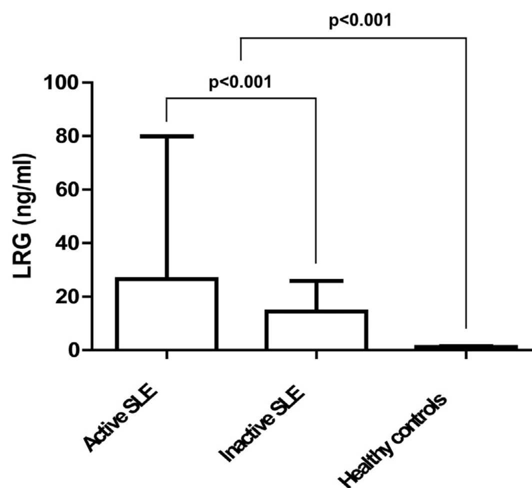

Fig. 1. Comparison of serum LRG in patients with SLE and in the healthy control group.
The median serum LRG was higher in patients with active and inactive SLE than in the control group. Data are expressed as the median, with the error bars indicating the interquartile range.
LRG, Leucine-rich alpha-2-glycoprotein; SLE, Systemic lupus erythematosus.

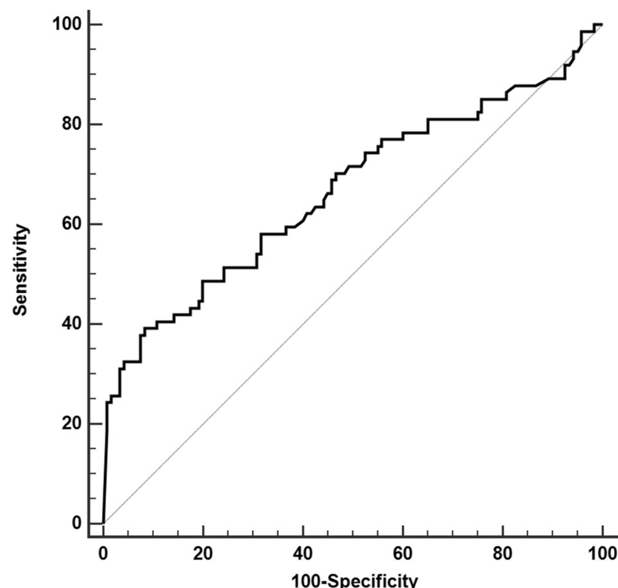

Fig. 2. Receiver operating characteristic curves for serum LRG to differentiate between active and inactive SLE.

2.4. Statistical analyses

Continuous variables are expressed as median (interquartile range), and categorical variables are expressed as numbers and percentages. Between-group differences in categorical variables were evaluated using the chi-squared or Fisher's exact tests, as appropriate for the data. Between-group differences in continuous variables were compared using the Mann-Whitney U test. Pearson's correlation analysis was used to evaluate the association between serum LRG and the SLEDAI-2 K and laboratory variables. Variables with a p-value < .05 on univariable logistic regression analysis were entered into a multivariable analysis to determine the odds ratio (OR) for each independent predictor of SLE activity. The optimal cut-off value of serum LRG for predicting active SLE was extrapolated by calculating the area under the receiver operator characteristic (ROC) curve. The relative risk (RR) of the cut-off value of serum LRG for active SLE and clinical manifestations of SLE

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