Original Article

Role of Cystatin C in Predicting Disease Activity and Flare-Up in Systemic Lupus Erythematosus: A Longitudinal Follow-Up Study

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Abstract

Background: We aimed to determine the sensitivity of serum cystatin C (Cys-C) in predicting lupus flare-up. **Methods:** In a longitudinal study, 77 patients were followed-up for up to 15 months. Cys-C, physician global assessment (PGA), and lupus activity index (SLEDAI) were recorded during each visit. Flare-up was defined as an increase ≥4 scores in SLEDAI compared to the last visit. The predictability of flare-up by Cys-C was evaluated by generalized linear-mixed effect model (GLMM) and generalized estimating equation (GEE). Predictive power of Cys-C, SLEDAI, and PGA was compared by the area under the curves (AUC) and application of receiver operating characteristic (ROC) curves. **Results:** Lupus flare-up was observed in 14 out of 77 patients on the 1st visit, 3 out of 41 patients on the 2nd visit, 2 out of 26 patients on the 3rd visit, 1 out of 14 patients on the 4th visit, and 1 out of 3 patients on the 5th visit. Mean Cys-C levels in patients with flare-up vs. those with no flare-up in the 1st, 2nd, and 3rd visits were 1769 vs. 1603 (P = 0.6), 5701 vs. 2117 (p = 0.2) and 1409 vs. 1731 (p = 0.9), respectively. Cys-C had lower predictive power than PGA and SLEDAI for either flare-up, active nephritis or SLEDAI in GLMM/GEE models. Cys-C also showed lower sensitivity (AUC = 0.701, 95%CI = 0.579-0.823, P = 0.003) than PGA and SLEDAI, to distinguish patients prone to flare-ups. **Conclusions:** Although Cys-C had some sensitivity for predicting flare-up, active nephritis or SLEDAI, its sensitivity was lower than that in PGA and SLEDAI.

Keywords: *Cystatin C, nephritis, systemic lupus erythematosus*

Introduction

Given the wide spectrum of clinical and laboratory manifestations of systemic lupus erythematosus (SLE), assessment, and monitoring of disease activity have been a challenge for physicians in both daily practice and research studies.[1] To meet this important need, many serologic, immunologic, genetic, and epigenetic markers have been developed. However, even those biomarkers with more specificity such as anti-double stranded DNA (anti-ds DNA) may not correlate with the disease activity in all occasions.[2,3] Therefore, ongoing efforts are being accomplished towards introducing new biomarkers to precisely capture disease activity.

Cystatin C (Cys C) is a low molecular cysteine protease inhibitor that is secreted by almost all nucleated cells in human being.[4] The relatively stable production, easy glomerular filtration, and fast metabolization by renal tubules, made it being recognized as an important compound to be able to more reliably measure glomerular filtration rate (GFR) than serum creatinine for the past three decades.[4-6] Moreover, Cys C, independent of renal function, was considered as an inflammatory marker[7] and a predictor for cardiovascular events and death.[8-10] In addition, its relationship with inflammatory diseases such as rheumatoid arthritis (RA) and SLE was investigated in recent years. Previous reports showed its association with autoantibodies, inflammatory markers and disease activity in patients with RA.[11,12] On the other hands, most studies about Cys C in SLE focused on its possible association with endothelial dysfunction and atherosclerosis[13-15] or its role in evaluating renal function and/or renal activity.[16-18] To the best of our knowledge, only one cross-sectional study has evaluated the association of Cys C and clinical manifestations in SLE.[19]

The aim of this longitudinal study was to investigate the sensitivity of Cys C to predict lupus flare, lupus activity, and active nephritis.

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Methods

Patients

Seventy-seven consecutive patients who fulfilled updated 1997 Criteria of American College of Rheumatology for SLE were eligible to enroll in this follow-up study.[20] Exclusion criteria included hyper/or hypothyroidisms, pregnancy, history of other autoimmune diseases, GFR <15 ml/min and active infections. Patients' data were accessed through medical records in Lupus Clinic, affiliated with the university. All patients signed the informed consent. The regional Ethics Committee approved the study (Code: 396142).

Clinical assessment and follow-up

Lupus nephritis (LN) was defined as clinical or biopsy-proven LN. The former was considered if the patient had urine protein >500 mg/day, red blood cell casts or >5 red blood cells/high power field.[20] The latter was categorized based on classification criteria of International Society of Nephrology/Renal Pathology Society.[21] On each visit, SLE disease activity index-2k (SLEDAI-2k) was calculated.[22] Damage was evaluated by Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI).[23] Flare was defined if the patient had an increase ≥4 scores in SLEDAI-2K compared to the previous visit.[24] Patients' next visit was based on either the physician's judgment or the patient's need, secondary to the aggravation of symptoms. The study period started on Dec 6th, 2016, and ended on Mar 12th, 2018. Clinical and laboratory parameters were recorded during each visit. The patients were evaluated in the follow-up visits by a rheumatologist (the corresponding author). In addition, he recorded disease activity according to physician global assessment (PGA). The PGA was scaled as 0 (no active disease), 1 (mild active disease), 2 (moderate active disease) and 3 (severe active disease).[25]

Laboratory assessment

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, urine analysis, blood urea nitrogen, serum creatinine, GFR, 24-hour urine protein, complement levels, anti-ds-DNA Ab, anticardiolipin Ab and anti-β2 glycoprotein I Ab were measured by standard protocols. All but antiphospholipid antibodies (which were measured on the first visit) were re-assessed on each visit. Cystatin C was measured on each visit by enzyme-linked immunosorbent assay kit (BioVendor, Laboratorni medicina a.s., Czech Republic) based on manufacturer's instructions.

Statistical methods

Patients were divided into two groups of disease flare-ups and remission. The Spearman correlation was employed to assess the correlation of disease flare-ups and other indices. Correlation indices less than 0.3, 0.3-0.7, and more than 0.7 were defined as weak, moderate, and strong correlations, respectively. Student t-test was employed to evaluate the mean difference of continuous indices between the two groups. For categorical indices, Chi-square test was used to evaluate the index distributions between the two groups. The probability of disease flare-ups vs. remission was evaluated by longitudinal analysis using generalized linear-mixed effect model (GLMM) and generalized estimating equations (GEE), adjusted for fixed effects of sex, age, and random effects of subjects. Information criteria to compare the models were based on Akaike's information criterion (AIC) in GLMM and Quasi-likelihood under Independence model Criteria (QIC) in GEE. Significant models with smaller AIC/QIC values fit better. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Predictive power of indices was compared through area under the curves (AUC) in plots of sensitivity vs. 1-specificity and application of receiver operating characteristic (ROC) curves. The larger the AUC, the higher the predictability of index. Data analyses were conducted using SPSS program (SPSS, Chicago, IL) and *P* value less than 0.05 was considered significant.

Results

Patients' characteristics

This study comprised 66 women and 11 men. The youngest patient aged 18 and the oldest aged 58 years [Table 1]. Patients were followed up for 1 to 15 months and they were visited between 1 to 6 times. Disease flare-up was observed in 14 out of 77 patients on the 1st visit, 3 out of 41 patients on the 2nd visit, 2 out of 26 patients on the 3rd visit, 1 out of 14 patients on the 4th visit, 1 out of 3 patients on the 5th visit, and 0 out of 1 patient on the 6th visit. There was no significant difference between women and men in terms of mean age (33.9 vs. 35.9 years, respectively), average BMI (24.3 vs. 26.7 kg/m^2, respectively), and Cys C levels (1865 vs. 1981 ng/ml, respectively). Women experienced significantly less frequent disease flare-ups

Table 1: Baseline laboratory values and demographics of patients recruited into the study and their baseline scores (*n*=77)

Patient Characteristics	Mean	Median	Minimum	Maximum
Age, years	34.2	33	18	58
Age at Diagnosis, years	25.8	25	11	53
Disease Duration, years	9.0	7.5	0.1	30
BMI, kg/m^2	24.6	24.1	16	36
SLEDAI, 1st visit	4.5	4	0	16
Baseline Laboratory values				
Proteinuria (mg/d)	451.6	146	35	4817
ESR	22.1	13	1	100
GFR	96.1	93.8	39	198
Cystatin C, ng/ml	1882	1437	404	21607

BMI: Body mass index, SLEDAI: Systemic Lupus Erythematosus Activity Index, ESR: Erythrocyte Sedimentation Rate, GFR: Glomerular Filtration Rate

than men (13/66 vs. 8/11, respectively, $P < 0.001$). Also, mean SLEDAI was significantly lower in women compared to men in all visits (the first visit for instance, 4.1 vs. 6.7, respectively, $P < 0.05$) and active nephritis was significantly less frequent in women (15/66 vs. 8/11, respectively, $P < 0.001$). Active nephritis in ≥two visits was observed in 3 women and 4 men. PGA of 1, 2, and 3 were observed in 13, 6, and 8 patients in the first visit, respectively. SDI of 1, 2, and 3 were observed in 18, 7, and 2 patients in the first visit, respectively.

Laboratory findings

Important baseline laboratory findings are presented in Table 1. Anti-ds-DNA, anticardiolipin and anti-β2 glycoprotein I antibodies were recorded in 55, 18, and 9 patients at baseline, respectively. Low C3 and low C4 levels were seen in 45 and 28 patients, respectively. Additional laboratory indices are accessible in Table 1.

Clinical manifestations

Overall, renal involvement was the most frequent organ treated (23 patients) followed by blood (11 patients), joints (2 patients), and skin (1 patient). Past and present clinical nephritis and biopsy-proven nephritis were recorded in 20 and 21 patients, respectively. Of the latter 21 ones, class III, IV, and V were observed in 5, 9, and 6 patients, respectively.

Medications

Hydroxychloroquine was the most frequent prescribed medication (66 patients) followed by prednisolone (37 patients), azathioprine (18 patients), mycophenolate mofetil (15 patients), tacrolimus (8 patients), cyclophosphamide (7 patients), and methotrexate (1 patients). The mean (SD) dosage of prescribed prednisolone in the first, second, and third visits were 7.4 (8.3), 6.6 (7.7), and 5.8 (3.1) mg/day, respectively. The mean cumulative dosage of prescribed prednisolone for the last 3 months in the first, second, and third visits were 677, 530, and 567 mg, respectively.

Three indices in terms of flare up

The correlations between disease flare-ups and other indices on the first visit are shown in Table 2. Flare-up, PGA, and active nephritis showed a positive weak correlation with Cys C. The correlation of Cys C with demographics, and all other symptoms, signs and medications were evaluated in all visits. A weak/moderate correlation of Cys C and the following variables were observed but the findings were not consistent in all visits: prednisolone dosage ($r = 0.84$ on the 1st visit), cyclophosphamide ($r = 0.47$ on the 1st visit), BUN ($r = 0.74$ on the 1st visit), creatinine ($r = 0.12$ on the 1st visit) and GFR ($r = -0.42$ on the 1st visit).

Distribution of PGA, mean SLEDAI, and mean Cys C between the two groups are compared in Table 3. Mean SLEDAI in the first and third visits were significantly higher in patients with flare-ups than in those on remission. Also, severe PGA scores (PGA >1) were significantly more prevalent in the first visit in patients with flare-ups than in those on remission [Table 3].

Longitudinal analyses

Disease flare-up was considered as the dependent variable and each index was considered as independent variable in GLMM and GEE models of longitudinal analyses [Table 4]. The models were adjusted for sex, age, and BMI. SLEDAI model revealed the smallest AIC among the three GLMM models and the smallest QIC among the three GEE models. It means SLEDAI better predicted SLE disease flare-ups than PGA and Cys C. Similar finding was repeated when active nephritis was considered as the dependent variable rather than disease flare-up in Cys C GLMM and GEE model. This means Cys C had less predictive power for lupus flare-up or lupus nephritis in our longitudinal models compared to SLEDAI and GPA. Also, when SLEDAI was considered as dependent variable, Cys C showed lower predictive power compared to GPA. Interestingly, sex was the significant predictor of active nephritis or SLEDAI in the corresponding models. Sensitivity analysis according to AUC and ROC are presented in Table 5 and Figure 1. Again, Cys C demonstrated the smallest AUC among the three indices, indicating the lowest ability of Cys C among the three indices to distinguish patients who were potentially prone to disease flare-ups [Table 5].

Discussion

To the best of our knowledge, this was the first longitudinal study evaluating the changes of Cys C in a group of SLE patients and assessing its association with disease flare-up.

Table 2: Spearman Correlation between flare-ups and other indices in the first visit

	PGA	SLEDAI	SDI	Active Nephritis	Flare-up	Cystatin C
PGA	1	0.656**	0.142	0.722*	0.720**	0.244*
SLEDAI	0.656**	1	0.131	0.669**	0.599**	0.172
SDI	0.142	0.131	1	0.090	0.157	-0.150
Active Nephritis	0.722*	0.669**	0.090	1	0.581**	0.230*
Flare-up	0.720**	0.599**	0.157	0.581**	1	0.197
Cystatin C	0.244*	0.172	-0.150	0.230*	0.197	1

PGA: Physician Global Assessment, SLEDA: Systemic Lupus Erythematosus Activity Index, SDI: Systemic Lupus Damage Index. *Correlation is significant at the 0.05 level (two-tailed). **Correlation is significant at the 0.01 level (two-tailed)

Cys C has been considered for many years as a more reliable and more precise reflection of renal function than serum creatinine.[4] This property is due to its constant production, freely filtration from renal glomeruli, solely metabolization in renal tissue as well as its independency from age, gender, and muscular mass.[14,26] However, it could be affected by several medical conditions such as thyroid diseases,[27] pregnancy[28], and other autoimmune diseases such as RA.[11] That is why patients with one of these conditions were excluded from the current study.

Although some studies, like ours, found no association between Cys C and age[29] sex,[30,31] BMI[31] and ethnicity,[29,32] some others demonstrated some corresponding associations.[33-35]

There is a growing interest to investigate the role of Cys C as a possible biomarker of inflammation in autoimmune diseases. For instance, two studies demonstrated the importance of Cys C as an index of inflammation in SLE patients, independent of renal function.[14,17] Our study also showed a weak correlation between Cys C and renal function in lupus patients, a finding that has been revealed before.[14,36]

Consistent with our results, most previous investigations[14,26,37-40] but not all,[27,29,41] demonstrated a positive correlation between corticosteroid and Cys C levels. The heterogeneity between these studies might be due to applying different standards to adjust kidney function.[27] It has been hypothesized that glucocorticoid

Table 3: Distribution of SLE indices between the two groups of flare-ups and remission

Visits	Index	Disease Flare-up		*P**
		Yes	No	
1st (*n*=77)	PGA >1, *n* (%)	10 (14%)	3 (4.2%)	0.0001
	SLEDAI, mean (SD)	8.3 (3.4)	3.3 (2.4)	0.0001
	Cystatin C, mean (SD)	1769 (790)	1603 (1137)	0.6
2nd (*n*=40)	PGA >1, *n* (%)	0 (0%)	2 (5%)	0.7
	SLEDAI, mean (SD)	5.0 (2.4)	3.45 (3.0)	0.4
	Cystatin C, mean (SD)	5701 (6192)	2117 (4296)	0.2
3rd (*n*=26)	PGA >1, *n* (%)	1 (3.8%)	1 (3.8%)	0.2
	SLEDAI, mean (SD)	10.0 (8.5	2.95 (1.9)	0.001
	Cystatin C, mean (SD)	1409 (509)	1731 (2832)	0.9

SLE: systemic lupus erythematosus, PGA: physician global assessment, SLEDAI: Systemic lupus erythematosus disease activity index

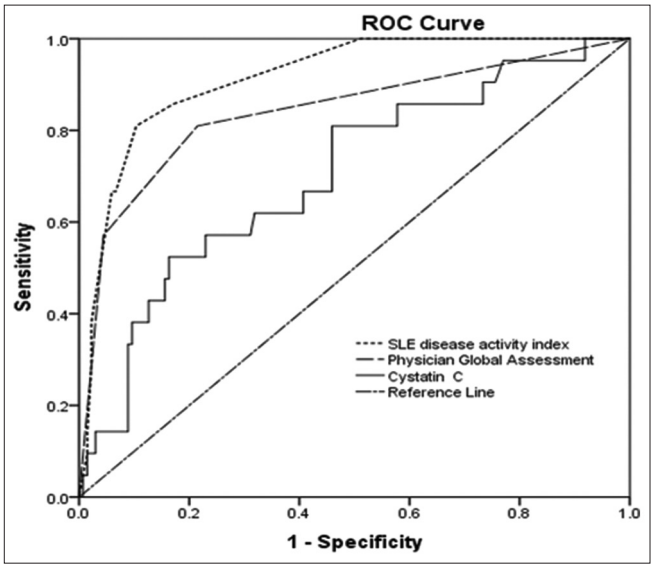

Figure 1: Sensitivity analyses of all three indices according to AUC and ROC

Table 4: Longitudinal analyses using GLMM and GEE. Disease flare-ups was the dependent variable. Three models were built to have either PGA, SLEDAI or Cystatin C as the main predictor. All six models were adjusted for age, sex and BMI

Model Terms	GLMM					GEE				
	Coefficient	OR	95% CI	*P*	AIC	Coefficient	OR	95% CI	*P*	QIC
PGA Model										
PGA	2.141	8.509	3.22-22.4	0.0001		2.141	8.509	3.71-19.5	0.0001	86.85
Sex=Female	-0.724	0.485	0.23-1.04	0.06	78.13	-0.724	0.485	0.20-1.16	0.10	
Age	-0.012	0.988	0.96-1.02	0.45		-0.012	0.988	0.95-1.03	0.60	
BMI	0.031	1.031	0.96-1.11	0.45		0.031	1.031	0.95-1.12	0.45	
SLEDAI Model										
SLEDAI	0.264	1.302	1.17-1.44	0.0001	70.34	0.264	1.302	1.12-1.50	0.0001	76.92
Sex=Female	-0.508	1.662	0.75-3.66	0.20		0.508	1.662	0.75-3.66	0.30	
Age	-0.015	0.985	0.95-1.02	0.40		-0.015	0.985	0.93-1.04	0.60	
BMI	0.068	1.070	0.98-1.17	0.15		0.068	1.070	0.99-1.15	0.06	
Cystatin C Model										
Cystatin C	0.00006	1.000	1.00-1.00	0.10	105.01	0.00006	1.000	1.00-1.00	0.005	102.5
Sex=Female	0.827	2.287	1.19-4.41	0.02		0.827	2.287	1.19-4.41	0.003	
Age	-0.004	0.996	0.97-1.02	0.80		-0.004	0.996	0.97-1.02	0.75	
BMI	0.029	1.030	0.96-1.10	0.40		0.029	1.030	0.96-1.11	0.45	

GLMM: Generalized Linear Mixed Effect Model, GEE: Generalized Estimating Equations, AIC: Akaike Information Criterion, QIC: Quasi-likelihood Under Independence model criteria, PGA: Physician Global Assessment, BMI: Body Mass Index, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Table 5: Area under curves (AUC) for all three indices

Index	AUC	95% Confidence Interval	*P*
PGA	0.841	0.733-0.949	0.0001
SLEDAI	0.915	0.858-0.972	0.0001
Cystatin C	0.701	0.579-0.823	0.003

AUC: Area Under the Curves, PGA: Physician Global Assessment, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

therapy might affect the Cys C levels by increasing the related gene transcription.[26] The associations between other immunosuppressive medications and Cys C have been inconsistent across different studies. Similar to our study, Gheita *et al*. showed a positive correlation between cyclophosphamide administration and Cys C level.[19] In addition, some researchers demonstrated an association between Cys C and cyclosporine,[42,43] whereas some other ones failed to show its correlation with tacrolimus, cyclosporine, or mycophenolate mofetil.[29,44]

Cys C had lower sensitivity than SLEDAI and PGA in predicting lupus flare-ups, active nephritis, or SLEDAI in our longitudinal models. AUC was applied to measure the ability of these three indices to discriminate the patients with and without lupus flare-up. By drawing ROC, Cys C showed also the lowest (far to the upper left corner) sensitivity compared to SLEDAI and PGA.

This study had some limitations. The results could have been more significant if we enrolled a control group. Also, the number of patients might have influenced the significance of findings. The larger the sample size, the higher the power of study to capture all aspects and determinants of disease flare-up. In addition, if the numbers of events (flare-up) were higher, we would be able to include more relevant variables such as smoking and CRP to build stronger regression models. Since about one third of patients had 3 visits during the follow-up, the findings could have been more conclusive if the duration of study was longer. Finally, as administered medications could modulate disease activity or the course of disease, the findings might be different if only incident patients were enrolled.

Conclusions

In summary, the current follow-up study concluded that Cys C might not be a reliable biomarker to predict disease activity or flare-up in patients with SLE. Longer-term follow-up studies with larger sample sizes are needed to precisely elucidate the association of Cys C and lupus flare-up.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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