

# Clinical Significance of Serum Cystatin C in SLE: A Potential Marker of Disease Damage Beyond Lupus Nephritis

Ibtisam M.A. Jali\* 

Internal Medicine and Rheumatology Department, King Abdulaziz University, Jeddah, Saudi Arabia.

\*Correspondence to: Ibtisam M.A. Jali (E-mail: ljali@kau.edu.sa)

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## Abstract

**Objective:** This work aimed to assess the serum level of cystatin C in systemic lupus erythematosus (SLE) patients and to determine the relation to disease characteristics and damage.

**Methods:** The study included 33 SLE patients presenting to the Internal Medicine and Rheumatology Department and Outpatient clinic, King Abdulaziz University, Saudi Arabia. The medical history, clinical examination, laboratory investigations and medications received by the patients were recorded. The systemic lupus international collaborating clinics damage index (SLICC-DI) was assessed. Serum cystatin C was measured using the immune-nephelometric method.

**Results:** The mean age of the patients was  $35.3 \pm 10.7$  years; 28 females and 5 males (F:M 5.6:1), disease duration  $5.5 \pm 3.1$  years and their age at onset was  $27.9 \pm 10.6$  years. Serum cystatin C level was significantly higher in patients with lupus nephritis (LN) ( $2.47 \pm 1.57$  mg/L vs  $v$  mg/L,  $P = 0.003$ ) and diabetes ( $4.92 \pm 0.05$  mg/L vs  $1.93 \pm 1.34$  mg/L;  $P < 0.0001$ ) and was lower in those with thyroid dysfunction ( $1.41 \pm 0.75$  mg/L vs  $2.3 \pm 1.59$  mg/L,  $P = 0.047$ ). There was a significant correlation between the serum cystatin C level with proteinuria ( $r = 0.57$ ,  $P = 0.011$ ) and with the SLICC-DI ( $r = 0.42$ ,  $P = 0.016$ ). Serum cystatin C could discriminate patients with LN at cut-off value of 0.904 mg/L with area under the curve of 0.765, sensitivity 87% and specificity 50%;  $P = 0.017$ .

**Conclusion:** The remarkable association between cystatin C and LN is confirmed and an emerging role is noted in reflecting the extent of disease damage. The likely association with diabetes and thyroid dysfunction should also be taken into consideration when deciding treatment regimens for LN patients.

**Keywords:** Cystatin C, systemic lupus erythematosus, lupus nephritis, thyroid dysfunction, SLICC-DI

## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiple organ involvement, especially the kidneys. However, the underlying mechanism remains unclear, and accurate biomarkers are still lacking.<sup>1</sup> Clinical and immunologic features of SLE may vary even within the same country. Even though autoantibodies are similarly present in patients worldwide, genetic and environmental factors may influence the different presentations and therapeutic regimens in lupus patients.<sup>2</sup>

Kidney damage is a frequent manifestation in SLE and the glomerular filtration rate (GFR) is a key test of renal function and is critical for diagnosis, stratification and response to treatment. An ultimate marker of GFR should be steadily produced, easily filtered, not reabsorbed or secreted by renal tubules and not metabolized or eliminated by extrarenal mechanisms. Creatinine is not an optimum marker of GFR as it is secreted by the tubules and is influenced by the muscle mass.<sup>3,4</sup>

Cystatin C is a low-molecular weight protein inhibitor of cysteine proteinases and was first isolated from sera of patients with autoimmune diseases. It inhibits papain, human cathepsin H and cathepsin B<sup>5</sup> and is produced at a constant rate regulated by a housekeeping gene.<sup>6</sup> Human cystatin C (hCC) is a basic protein that is expressed and secreted by a wide variety of human cells and tissues and is ubiquitously found in body fluids and an increased level could be associated with cases of idiopathic pulmonary fibrosis.<sup>7</sup> Increased cystatin concentrations are also associated with cardiovascular (CV) risk, independent of conventional measures of renal function.<sup>8</sup>

Cystatin C is a protein produced by all nucleated cells, freely filtered by the glomerulus, does not return to the bloodstream, is not secreted by the renal tubules without any extrarenal elimination.<sup>3,6,9</sup> Such bright features make serum cystatin C measurement an excellent diagnostic test for detecting patients with subclinical renal dysfunction.<sup>10</sup> It has characteristics of an ideal endogenous marker, being similar or even superior to serum creatinine.<sup>11</sup> Besides serum creatinine, which is a routine biomarker for evaluation of GFR, it is well established that serum hCC is also a valuable earlier marker of acute kidney injury (AKI).<sup>7</sup> The relevance of determining cystatin C for diagnosis in CKD is included in the international KDIGO (Kidney Disease Improving Global Outcomes) guidelines.<sup>12</sup> Certain factors may influence the levels of cystatin C including smoking, obesity, gender, steroids, age and diabetes.<sup>13</sup> In fact SCysC is not only a good marker of renal function, but may serve in predicting SLE progress.<sup>11,14</sup> One of the major drawbacks of creatinine is the blind range as it does not increase until 50% of the kidney deteriorates. Meanwhile, cystatin C is emerging as an attractive promising biomarker due to superior features over creatinine. Its levels are elevated as soon as any mild defect in the kidney occurs and is influenced by several non-renal diseases which provide an additional prognostic value.<sup>15</sup> Although cystatin C had some sensitivity for predicting flare-up and active nephritis, its sensitivity was lower than that the physicians global assessment (PGA) and SLE disease activity index (SLEDAI).<sup>16</sup>

This work aimed to assess the serum level of cystatin C in SLE patients and to determine the relation to disease characteristics and damage.

## Patients and Methods

The study included 33 SLE patients fulfilling the 2012 systemic lupus international collaborating clinics (SLICC) classification criteria<sup>17</sup> presenting to the Internal Medicine and Rheumatology Department and Outpatient clinic, King Abdulaziz University, Saudi Arabia. The study was approved by the ethical committee of King Abdulaziz University (REC no. 97–24) and was in accordance with the principles of the Declaration of Helsinki. Informed consents are provided by all patients.

The medical history, clinical examination, laboratory investigations and medications received by the patients. The SLICC damage index (SLICC DI)<sup>18</sup> was assessed.

Serum cystatin C was measured using the immune-nephelometric method (N Latex Cystatin C Assay, BN II Systems, Siemens Healthcare Diagnostics, Erlangen, Germany) with a reference range of 0.62–1.11 mg/L.

## Statistical Analysis

Statistical Package for Social Science (SPSS) program version 25 was used for analysis of data. Data was presented as number, and frequency (%) or mean  $\pm$  SD, range and median. Mann-Whitney test was used for analysis of two quantitative non-normally distributed data and Spearman's correlation test considered. Receiver operating characteristic (ROC) curve was constructed to reveal the potential of cystatin C to discriminate lupus nephritis. Results were adapted for missing variables. Significance was set at  $P < 0.05$ .

## Results

The mean age of the 33 patients was  $35.3 \pm 10.7$  years; 28 females and 5 males (F:M 5.6:1), disease duration  $5.5 \pm 3.1$  years and age at onset  $27.9 \pm 10.6$  years.; 3 were of juvenile onset. Serum cystatin C level according to the presence and absence of characteristics in patients are presented in Table 1 and Figure 1. Of the 7 patients with thyroid disorders, 6 were hypothyroid and only one was hyperthyroid. The mean serum cystatin C level tended to be higher in males yet similar according to gender ( $n = 5$ ,  $2.76 \pm 1.42$  vs  $n = 28$ ,  $1.99 \pm 1.49$  mg/l,  $P = 0.32$ ); In Saudi patients ( $n = 12$ ) ( $2.3 \pm 1.78$  mg/l) the level was also comparable to non-Saudi ( $n = 21$ ) ( $2 \pm 1.34$ ) ( $P = 0.62$ ). The levels tended to be higher yet matching according to mortality ( $n = 12$ ,  $2.63 \pm 1.72$  mg/l vs  $n = 21$ ,  $1.81 \pm 1.29$  mg/l;  $P = 0.17$ ).

Correlations of certain parameters with cystatin C level are presented in Table 2. Significant correlation of serum cystatin C with SLICC-DI is presented in Figure 2. The ROC curve of serum cystatin C to discriminate patients with and without lupus nephritis is shown in Figure 3. At cut-off value of 0.904 with area under the curve of 0.765, sensitivity 87% and specificity 50%;  $P = 0.017$ .

## Discussion

Lupus nephritis (LN) is a potentially devastating outcome of SLE and identifying reliable, non-invasive methods to assess the kidneys is a compelling demand.<sup>19</sup> The information concerning non-invasive, easily obtainable, and accurate

Table 1. Cystatin C level according to the presence and absence of characteristics in systemic lupus erythematosus patients

Parameter mean $\pm$ SD	Characteristics in SLE patients (n = 33)		
	present/yes	absent/no	P-value
Diabetes (n = 2)	4.92 $\pm$ 0.05	1.93 $\pm$ 1.34	<b>&lt;0.0001</b>
Hypertension (n = 15)	2.45 $\pm$ 1.34	1.83 $\pm$ 1.58	0.23
Thyroid disorder (n = 7)	1.41 $\pm$ 0.75	2.3 $\pm$ 1.59	<b>0.047</b>
Photosensitivity (n = 2)	0.83 $\pm$ 0.26	2.19 $\pm$ 1.5	<b>0.003</b>
Renal (n = 23)	2.47 $\pm$ 1.57	1.29 $\pm$ 0.88	<b>0.01</b>
Arthritis (n = 1)	0.79	2.15 $\pm$ 1.49	-
CVS (n = 7)	2.67 $\pm$ 1.24	1.96 $\pm$ 1.53	0.22
DVT (n = 4)	2 $\pm$ 0.82	2.12 $\pm$ 1.57	0.81
Hematological (n10)	1.95 $\pm$ 0.94	2.18 $\pm$ 1.68	0.62
Neuropsychiatric (n = 25)	2.23 $\pm$ 1.56	1.72 $\pm$ 1.25	0.36
Consumed C3 (n = 14)	2.61 $\pm$ 1.36	1.76 $\pm$ 1.59	0.12
Consumed C4 (n = 5)	1.62 $\pm$ 1.34	2.25 $\pm$ 1.57	0.39
Anti-dsDNA (n = 20)	1.85 $\pm$ 1.27	2.31 $\pm$ 1.67	0.43
Aspirin (n = 8)	2.22 $\pm$ 1.46	2.07 $\pm$ 1.53	0.8
Warfarin (n = 8)	2.18 $\pm$ 1.35	2.09 $\pm$ 1.55	0.87
Heparin (n = 19)	2.66 $\pm$ 1.57	1.36 $\pm$ 0.99	<b>0.007</b>
Steroids (n = 19)	2.39 $\pm$ 1.55	1.72 $\pm$ 1.35	0.2
HCQ (n = 25)	2.12 $\pm$ 1.54	2.09 $\pm$ 1.41	0.96
AZA (n = 13)	2.59 $\pm$ 1.99	1.8 $\pm$ 0.98	0.2
MMF (n = 3)	1.92 $\pm$ 1.12	2.13 $\pm$ 1.53	0.79
RTX (n = 5)	1.79 $\pm$ 1.24	2.17 $\pm$ 1.54	0.56
CYC (n = 5)	2.24 $\pm$ 1.18	2.09 $\pm$ 1.55	0.81

SLE: systemic lupus erythematosus; CVS: cardiovascular disease; DVT: deep venous thrombosis; anti-dsDNA: anti-double stranded deoxyribonucleic acid; C: complement; HCQ: hydroxychloroquine; AZA: azathioprine; MMF: mycophenolate mofetil; RTX: rituximab; CYC: cyclophosphamide; Bold values are significant at  $P < 0.05$ .

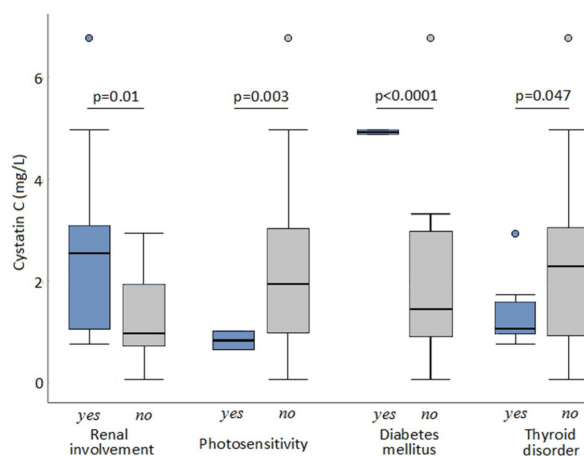


Fig. 1 Serum cystatin C level in systemic lupus erythematosus patients with and without renal involvement, photosensitivity, diabetes mellitus and thyroid disorder.

biomarkers for diagnosis of LN is extremely limited.<sup>20</sup> Serum cystatin C is an imperative marker of LN and helps in predicting the renal biopsy class.<sup>19</sup> Cystatin C has a strong tie with GFR and a more significant clinical prognosis than creatinine.

Table 2. Correlation of serum cystatin C level with disease characteristics in systemic lupus erythematosus patients

Parameter r (P)	Cystatin C in SLE (n = 33)
Age (years)	0.13 (0.47)
Disease duration (years)	-0.2 (0.33)
Age at onset (years)	-0.02 (0.93)
Hemoglobin (g/dl)	-0.47 (0.006)
TLC ( $\times 10^3/\text{mm}^3$ )	0.17 (0.36)
Platelets ( $\times 10^3/\text{mm}^3$ )	-0.11 (0.53)
Proteinuria (g/24hr)	0.57 ( <b>0.011</b> )
C3 (mg/dl)	-17 (0.37)
C4 (mg/dl)	0.04 (0.85)
ANA titre	0.23 (0.2)
Anti-dsDNA level (IU/ml)	-0.2 (0.28)
SLICC-DI	0.42 ( <b>0.016</b> )

SLE: systemic lupus erythematosus; TLC: total leucocytic count; C: complement; ANA: anti-nuclear antibodies; anti-dsDNA: anti-double stranded deoxyribonucleic acid; SLICC-DI: systemic lupus international collaborating clinics damage index; Bold values are significant at  $P < 0.05$ .

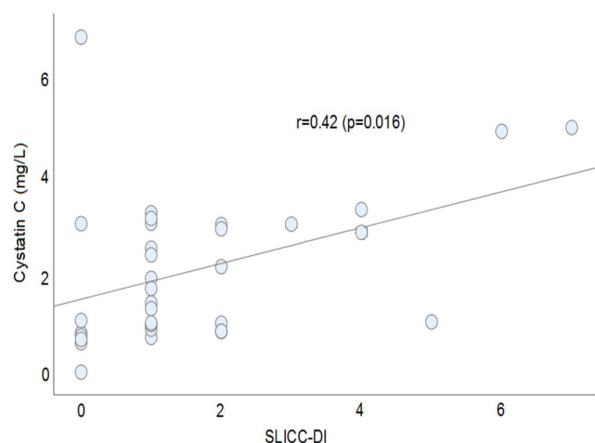


Fig. 2 Correlation between cystatin C level and systemic lupus international collaborating clinics damage index (SLICC-DI) in systemic lupus erythematosus patients.

It is a better marker to define chronic kidney disease (CKD), allowing more accurate classification and risk stratification, compared with creatinine.<sup>20</sup> Serum hCC is a valuable and more accurate marker of GFR than the widely used serum creatinine and may represent an alternative for the early assessment of AKI.<sup>7</sup>

In this work, cystatin C was significantly increased in SLE patients especially those with LN. In line, cystatin C, but not other measures of renal function, was significantly higher in SLE patients.<sup>8</sup> Furthermore, serum cystatin C was significantly increased in SLE patients especially those with LN.<sup>21,22</sup> Cystatin C is produced from neutrophil activation and is prominently upregulated in SLE patients with proteinuria and anti-dsDNA positivity.<sup>1</sup>

It is necessary to determine the best equation for the GFR in patients with LN, as there are different formulas for patients with diabetes or CKD, but not for rheumatic diseases, which have different implications for renal damage.<sup>4,23</sup> However, it

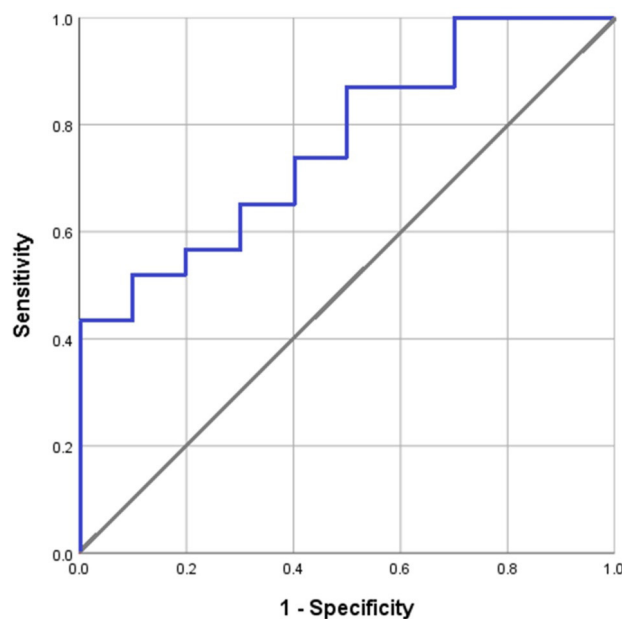


Fig. 3 Receiver operating characteristic (ROC) curve to discriminate systemic lupus erythematosus patients with and without lupus nephritis. At cut-off value of 9.04 with area under the curve of 0.765, sensitivity 87% and specificity 50%;  $P = 0.017$ .

has been reported that serum cystatin C may be influenced by low grade inflammation and renal dysfunction, and thus should not supplant current assessment of renal dysfunction in SLE.<sup>21</sup>

In this work, apart from the relation with LN and photosensitivity, although in a low number of cases, there was no significant relation between serum cystatin C level and other clinical manifestations. Despite the reports that cystatin C is an independent predictor of CV risk, considering only patients without any renal impairment ruled out any association.<sup>24</sup> In harmony, in a study on Egyptian SLE patients, there was no significant difference in the cystatin C level between those with and without clinical manifestations except being higher in those with mucocutaneous features.<sup>19</sup>

Currently, in spite the low number of diabetic patients, yet the serum levels of cystatin C were significantly high. The association between serum cystatin C level and vascular outcomes such as myocardial infarction, stroke, end-stage renal disease and diabetic retinopathy was for a long time not fully elucidated in diabetes and prediabetes; however, in a study from the UK on 85,371 participants with prediabetes and diabetes, serum cystatin C refined the risk stratification for mortality and vascular outcomes among such a vulnerable group of patients.<sup>25</sup> Cystatin C dysregulations could be used as a risk indicator for diabetes and as a warning sign for accelerated risk of mortality.<sup>26</sup> The newly suggested serum creatinine-to-cystatin C ratio (sCr/sCysC) may aid in predicting adverse outcomes in many diseases including diabetes.<sup>27</sup> Serum cystatin C was a self-regulating factor in patients with combined type 2 diabetes and CKD.<sup>28</sup>

In the present study, patients with thyroid dysfunction were mostly hypothyroid and the serum cystatin C level was significantly lower compared to those without a thyroid disorder. The progression of chronic kidney disease (CKD) is concomitant with complications, including thyroid dysfunction<sup>29</sup> and whether the performance of cystatin C is affected

by thyroid hormones has raised concern in critically ill patients.<sup>30</sup> Cystatin C levels are affected by the thyroid state being increased in hyperthyroidism and decreased in hypothyroidism.<sup>31,32</sup> It is established that thyroid dysfunction has a major impact on cystatin C levels and therefore, thyroid function has to be considered when it is used as a marker of kidney function.<sup>31</sup> However, the thyroid function had no significant impact on the diagnostic and predictive accuracy of cystatin C in detecting AKI in ICU patients.<sup>30</sup> In a study aiming to determine the impact of non-renal diseases on levels cystatin C, diabetes, thyroid and cardiac dysfunctions had a clear effect, whereas age, gender and smoking habit have none.<sup>15</sup>

Patients in this work receiving *heparin* had a significantly higher level of cystatin C compared to those not. A recent report indicated that the cystatin C binds to heparin sulphate (HS) in a pH-dependent manner thus modulating and finely tuning the inhibitory potential of hCC on papain which in turn may reflect an abnormal regulation of cathepsins.<sup>7</sup>

In the current work, the serum cystatin C level was not affected by the *other medications* received by the patients. Although it has been shown that glucocorticoids have an influence on serum cystatin C levels, such effect was not observed in LN patients on steroids.<sup>11</sup> The value of having the serum level of cystatin C not showing any significant relation to the medications received makes it a good marker of renal function in patients with LN as the renal level of this marker is thus not modified by drugs including corticosteroids.<sup>4</sup>

The disease *damage* in the present study significantly correlated with serum cystatin C level and the level of serum cystatin tended to be higher in relation to the frequency of *mortality*. It has been reported that cystatin C is a hopeful marker for monitoring organ damage in SLE [Huang] and others delineated the significant relation between cystatin C and the SLICC-DI [Garcia-Garcia]. Moreover, levels of cystatin C was significantly inversely related to the inner diameter of brachial artery in SLE patients.<sup>33</sup> In a study on three renal

biomarkers, serum cystatin C, urinary neutrophil gelatinase-associated lipocalin (UNGA) and N-acetyl-beta-D-glucosaminidase (UNAG) were remarkably increased but only serum cystatin C would best correlate with the SLICC-DI.<sup>19</sup>

Cystatin C had a notable *discriminative potential* for SLE patients with and without LN at a cut-off value of 9.04 mg/L with a high sensitivity (87%) and moderate specificity (50%). The separately detected cystatin C (CysC) (eGFR<sub>CysC</sub>) and C1q were superior to the conventional biomarkers urea, creatinine and eGFR<sub>creat</sub> in the diagnosis of LN. Moreover, although the combined estimation had the greatest diagnostic performance, the joint utilization of CysC and C1q could be prioritized for rapid discrimination of LN if the economic burden is taken into consideration.<sup>22</sup>

The small sample size and cross sectional study design form limitations to this work and a larger scale longitudinal study design is recommended to confirm the reached findings. Including a control group and extended variables such as the disease activity as well as evaluating the creatinine-cystatin C ratio may also be considered in future work.

In conclusion, this work, in addition to confirming the established link of cystatin C with LN, has an emerging role in reflecting the extent of disease damage. The likely association with diabetes and thyroid dysfunction should also be taken into consideration when deciding treatment regimens for LN patients.

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## Conflict of Interest

The authors declare no conflict of interest. ■

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