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A CROSS-SECTIONAL STUDY ON THE CLINICAL SIGNIFICANCE OF CREATININE, BLOOD UREA, AND CYSTATIN C IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS.

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ABSTRACT

Background

The study aims to determine the clinical significance of renal biomarkers—specifically serum creatinine, cystatin C, and blood urea—in patients diagnosed with systemic lupus erythematosus (SLE), with a particular focus on evaluating their association with renal involvement and disease severity.

Methods

A total of 140 participants were enlisted, 70 of whom were SLE patients and 70 of whom were age- and sex-matched controls. Along with proteinuria levels, serum levels of creatinine, cystatin C, and blood urea were important variables that were assessed. Statistical analysis was also done to determine significance.

Results

Serum cystatin C levels were significantly elevated in SLE patients (mean 1.25 mg/L) compared to controls (mean 0.95 mg/L), $p < 0.001$. Similarly, serum creatinine (mean 1.02 mg/dL in SLE vs. 0.88 mg/dL in controls, $p = 0.003$) and blood urea levels (mean 35.6 mg/dL in SLE vs. 28.4 mg/dL in controls, $p < 0.001$) were higher in SLE patients. Proteinuria levels were markedly higher in SLE cases (mean 225 mg/day) compared to controls (mean 15 mg/day), $p < 0.001$. Serum cystatin C levels and proteinuria levels in SLE patients exhibited a favorable association, according to Pearson correlation analysis ($r = 0.68$, $p < 0.001$).

Conclusion

Serum creatinine, cystatin C, and blood urea are elevated in SLE patients with lupus nephritis, with cystatin C showing a strong association with proteinuria levels, indicating its potential as a sensitive biomarker for early renal impairment. These findings underscore the importance of incorporating cystatin C in routine assessments for better management of lupus nephritis.

Recommendations

Further, longitudinal studies are recommended to validate the predictive value of cystatin C and explore its role in guiding therapeutic interventions in lupus nephritis. The routine use of these indicators in clinical practice can help patients with SLE manage their renal involvement and detect it early.

Keywords: *Lupus nephritis, Systemic lupus erythematosus, Cystatin C, Creatinine, Blood urea nitrogen*
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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune illness in which the body's tissues are attacked by the immune system, resulting in tissue damage and widespread inflammation. Lupus nephritis is a severe manifestation of SLE. When SLE affects the kidneys, it can result in lupus nephritis, which can cause inflammation and possibly even failure if left untreated. For patients with lupus nephritis, early identification and monitoring of kidney function are essential to minimize irreparable damage and maximize therapeutic results.

Creatinine, Cystatin C, and blood urea nitrogen are three essential biomarkers that are used to evaluate kidney function in individuals with lupus nephritis (BUN). These biomarkers offer important new information about the course of the disease, renal function, and the efficacy of treatment.

All nucleated cells generate the low molecular weight protein cystatin C, which has a strong inhibitory effect on

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cysteine proteases. Cystatin C is a more accurate marker for measuring glomerular filtration rate (GFR) than creatinine since it is less affected by age, sex, and muscle mass. This is especially true for patients with different amounts of muscle mass. Increased Cystatin C levels are linked to the development of lupus nephritis and are indicative of impaired kidney function. Studies have demonstrated that Cystatin C is a sensitive marker for early renal impairment detection in patients with SLE, even before notable increases in creatinine levels [1].

A byproduct of muscle metabolism known as creatinine is another important kidney function indicator. Urine is the result of the kidneys filtering it out of the blood. Increased levels of creatinine in the serum indicate compromised renal function. Although creatinine is a widely used and convenient marker, it has limitations, such as variability due to factors like age, sex, and muscle mass. In lupus nephritis patients, monitoring creatinine levels helps assess the extent of kidney damage and the response to treatment [2].

The amount of nitrogen in the blood as urea, a consequence of protein breakdown, is measured by blood urea nitrogen (BUN). Since the kidneys are in charge of urea excretion, elevated BUN levels may be a sign of impaired renal function. BUN, however, is less precise than creatinine and Cystatin C since it is affected by several variables, including hydration, liver function, and food. Notwithstanding these drawbacks, BUN is still a helpful indicator for assessing renal function and tracking the development of lupus nephritis [3].

Cystatin C, creatinine, and BUN are essential biomarkers for assessing kidney function in lupus nephritis patients with SLE. Each biomarker offers unique advantages and, when used together, provides a comprehensive evaluation of renal health, facilitating early detection, monitoring, and management of lupus nephritis.

The study aims to investigate the clinical significance of renal biomarkers, including serum cystatin C, creatinine, and blood urea, in patients diagnosed with SLE, with a specific focus on evaluating their association with renal involvement and disease severity.

METHODOLOGY

Study Design

A cross-sectional, prospective, and observational design.

Study Setting

The research was conducted at Jawahar Lal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, spanning from March 2023 to April 2024.

Participants

A total of 140 subjects were involved in the study, including 70 patients diagnosed with SLE and 70 age and sex-matched controls.

Inclusion and Exclusion Criteria

Inclusion criteria stipulated a confirmed diagnosis of SLE. Exclusion criteria comprised the presence of kidney diseases with etiologies other than lupus, diabetes, pregnancy, and thyroid disease.

Bias

Potential biases were minimized through adherence to stringent study protocols and uniform data collection procedures.

Variables

The primary variables of interest were creatinine, cystatin C, blood urea, and proteinuria levels in SLE patients.

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z2 \times p \times (1-p)}{E2}$$

Where:

- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

Data Collection

Serum creatinine was measured using the enzymatic approach in the Mespa xl 240, serum cystatin C levels were ascertained using the Nephelometric immunoassay method, blood urea was measured using the urease single-step method in the auto analyzer ERBA 640, and proteinuria was identified using the Sulfo-salicylic acid method.

Some of the variables evaluated were serum cystatin C levels (reference values: 0.55–1.15 mg/L for individuals under 50 and 0.63–1.44 mg/L for individuals over 50), creatinine levels ascertained by the modified Jaffe's method (reference value: 0.5–1.1 mg/dL), and blood urea levels ascertained by the urease method.

Statistical Analysis

For analysis, measurement data were merged into a master chart. The statistical analysis was performed using SPSS version 15.0 and Microsoft Excel 2007. In statistical analysis, continuous data were expressed as mean and standard deviation (SD), and categorical values as numbers (%). A five percent threshold for relevance was set.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

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RESULT

Table 1: Socio-demographic profile

Variable	SLE Cases (n=70)	Controls (n=70)
Mean Age (years)	35.4 ± 8.2	34.8 ± 7.9
Gender (Female)	60 (85.7%)	58 (82.9%)
Education Level		
- Primary School	10 (14.3%)	12 (17.1%)
- High School	30 (42.9%)	28 (40.0%)
- College Degree	20 (28.6%)	22 (31.4%)
- Postgraduate	10 (14.3%)	8 (11.4%)
Occupation		
- Employed	40 (57.1%)	42 (60.0%)
- Unemployed	20 (28.6%)	18 (25.7%)
- Student	10 (14.3%)	10 (14.3%)

The study included 140 patients in total, 70 of whom were age and sex-matched controls and 70 of whom were SLE cases. The average age of SLE cases was 35.4 (± 8.2) years, whereas the average age of controls was 34.8 (± 7.9) years. Age and sex distribution differences between SLE patients and controls were not statistically significant ($p > 0.05$).

Table 2: Comparison of mean serum creatinine, blood urea, and cystatin C between two groups

Variables	SLE cases	Controls
Mean serum creatinine (mg/dL)	1.02 ± 0.18	0.88 ± 0.15
Mean blood urea (mg/dL)	35.6 ± 8.9	28.4 ± 6.7
Mean cystatin C (mg/L)	1.25 ± 0.35	0.95 ± 0.22

With an average level of 1.25 mg/L (± 0.35) in SLE cases and 0.95 mg/L (± 0.22) in controls, serum cystatin C levels were considerably higher in SLE patients than in controls ($p < 0.001$). Likewise, there was a statistically significant difference ($p = 0.003$) in the serum creatinine levels between SLE patients (mean = 1.02 mg/dL, ± 0.18) and controls (mean = 0.88 mg/dL, ± 0.15). In addition, blood urea levels were higher in SLE patients than in controls (mean = 28.4 mg/dL, ± 6.7; $p < 0.001$), with an average level of 35.6 mg/dL (± 8.9). Additionally, there was an extremely significant variation ($p < 0.001$) in the levels of proteinuria between SLE cases (mean = 225 mg/day, ± 65) and controls (mean = 15 mg/day, ± 5).

Table 3: Comparison of all renal parameters

Parameters	SLE cases	Controls
Mean serum creatinine (mg/dL)	1.02 ± 0.18	0.88 ± 0.15
Mean blood urea (mg/dL)	35.6 ± 8.9	28.4 ± 6.7
Mean cystatin C (mg/L)	1.25 ± 0.35	0.95 ± 0.22
Mean proteinuria (mg/day)	225 ± 65	15 ± 5

A positive correlation ($r = 0.68$, $p < 0.001$) was found by Pearson correlation analysis between serum levels of cystatin C and proteinuria in patients with SLE, suggesting a possible link between cystatin C and kidney involvement in SLE. Serum cystatin C levels and serum creatinine levels, however, did not significantly correlate ($r = 0.12$, $p = 0.27$).

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Table 4: Logistic regression analysis

Predictor Variable	Beta Coefficient	Standard Error	Odds Ratio (OR)	95% CI	p-value
Serum Cystatin C	0.89	0.21	2.45	1.78 - 3.36	<0.001
Age (years)	0.05	0.12	1.05	0.84 - 1.32	0.69
Gender (Female)	-0.12	0.18	0.89	0.65 - 1.22	0.45
Disease Duration (years)	0.03	0.09	1.03	0.88 - 1.21	0.72
Constant	-1.72	0.42	-	-	<0.001

Moreover, serum cystatin C levels were found to be significantly correlated with the presence of proteinuria in SLE patients (OR = 2.45, 95% CI: 1.78-3.36, $p < 0.001$), according to logistic regression analysis that controlled for age, sex, and length of disease. This suggests that cystatin C has an independent predictive value for renal involvement in SLE.

DISCUSSION

Out of the 140 participants in the study, 70 had been diagnosed with SLE, while the remaining subjects were evenly distributed in terms of age and sex as controls. The age and sex distributions of the SLE cases and controls did not differ significantly ($p > 0.05$).

With an average level of 1.25 mg/L (± 0.35) in SLE cases and 0.95 mg/L (± 0.22) in controls, serum cystatin C levels were significantly higher in SLE patients than in controls ($p < 0.001$).

In a similar vein, SLE patients had greater blood urea (35.6 mg/dL, ± 8.9) and serum creatinine (1.02 mg/dL, ± 0.18) than controls (0.88 mg/dL ± 0.15; 28.4 mg/dL ± 6.7), with statistically significant variations ($p < 0.001$ for blood urea and $p = 0.003$ for serum creatinine).

Serum cystatin C levels and proteinuria levels in SLE patients showed a positive correlation ($r = 0.68$, $p < 0.001$) according to Pearson correlation analysis, pointing to a possible link between cystatin C and renal involvement in SLE. Serum creatinine and cystatin C levels, however, did not significantly correlate ($r = 0.12$, $p = 0.27$).

Serum cystatin C levels continued to be significantly correlated with the presence of proteinuria in SLE patients (OR = 2.45, 95% CI: 1.78-3.36, $p < 0.001$), according to logistic regression analysis adjusted for age, sex, and length of disease. This suggests that cystatin C has an independent predictive value for renal involvement in SLE.

The study suggests that serum cystatin C is a valuable biomarker for assessing renal involvement in SLE. Its levels are significantly elevated in SLE patients and strongly correlate with proteinuria. The association of cystatin C with renal involvement remains significant irrespective of age, gender, or duration of illness. While these findings are promising, further long-term studies are needed to confirm the predictive value and clinical utility of cystatin C in managing renal disease in SLE patients.

Numerous investigations investigating the clinical importance of blood urea, creatinine, and Cystatin C in lupus nephritis patients with SLE have yielded important insights into the diagnostic and prognostic value of these markers.

Because Cystatin C is independent of variables like gender and muscle mass, it is a more reliable indicator of renal function than creatinine, according to a South Indian case-control study. This study emphasizes Cystatin C's superiority when evaluating kidney function in patients with lupus nephritis [4].

Serum Cystatin C alone or in combination with complement component 1q surpassed more conventional biomarkers like urea and creatinine, according to research on the diagnostic efficacy of these two biomarkers. This suggests that Cystatin C and C1q are better at identifying lupus nephritis that is actively progressing [5].

Cystatin C is a valid marker for pre-diagnosis of kidney failure, according to an assessment of kidney failure tests using the SLEDAI and Cys. C Index. Cystatin C also shown strong relationships with creatinine levels in individuals with lupus nephritis. This highlights Cystatin C's potential for early detection and surveillance [6].

Positive relationships were discovered between Cystatin C levels, disease activity, and renal function tests in a study that measured blood Cystatin C in patients with lupus nephritis. According to the results, measuring Cystatin C is helpful, although it might not have a greater prognostic value than creatinine on its own before renal biopsy [7].

Studies on the connection between SLE patients' disease activity and the cystatin C/creatinine ratio have shown that a larger ratio corresponds to a higher level of disease activity. This ratio offers useful information beyond renal function alone and may be used as an independent indicator of disease activity [8].

Another study looking at the urine ferritin/creatinine ratio in lupus nephritis showed that this ratio can be used as a biomarker for kidney damage in lupus nephritis since it corresponds positively with disease activity indicators [9].

Cystatin C is useful in early illness monitoring because it has a higher sensitivity in detecting early renal function deterioration than serum creatinine and blood urea nitrogen, according to a review of clinical indexes and pathological classifications in patients with lupus nephritis [10].

It was discovered that proteinuria in lupus nephritis may be predicted with a combination of urine monocyte chemoattractant protein 1 (uMCP-1) and tumor necrosis factor-like weak inducer of apoptosis (uTWEAK). These biomarkers may be useful as possible indications of

proteinuria and correlate with the severity of the disease [11].

Significant correlations were identified between urine podocyte levels and conventional markers like creatinine and urea in a study looking into the biomarker for lupus nephritis. These findings imply that urinary podocyte levels may be a noninvasive biomarker for the early diagnosis and monitoring of kidney damage in lupus nephritis [12].

CONCLUSION

The study provides evidence of elevated serum cystatin C levels in SLE patients, which are positively associated with the presence of proteinuria, indicating potential renal involvement. These findings highlight the potential utility of serum cystatin C as a biomarker for lupus nephritis. However, further longitudinal studies are warranted to validate these findings and assess the clinical utility of cystatin C in the management of SLE-associated renal disease.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

Further, longitudinal studies are recommended to validate the predictive value of cystatin C and explore its role in guiding therapeutic interventions in lupus nephritis. The routine use of these indicators in clinical practice can help patients with SLE manage their renal involvement and detect it early.

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List of abbreviations

SLE - Systemic Lupus Erythematosus
GFR - Glomerular Filtration Rate
BUN - Blood Urea Nitrogen
CI - Confidence Interval
OR - Odds Ratio
ERBA - A brand of laboratory equipment
MCP-1 - Urine Monocyte Chemoattractant Protein 1
tweak - Urine Tumor Necrosis Factor-like Weak Inducer of Apoptosis

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Conflict of interest

The authors have no competing interests to declare.

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