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Exploring Uropathogenic Bacteria and Measuring Serum IL-34 and IL-35 Levels in Women Affected by Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus is an autoimmune disease occurs when the immune system mistakes self-tissue for foreign antigens, it causes organ tissue destruction in Systemic lupus erythematosus risk factors include interleukin biomarkers and urinary tract infections. The goal of this study was to identify uropathogenic bacteria in systemic lupus erythematosus patients, which is essential for avoiding serious complications. Additionally, serum levels of interleukin -34 and interleukin-35 in Systemic lupus erythematosus patients serve as a predictor biomarkers for systemic lupus erythematosus diagnosis. 65 women with systemic lupus erythematosus compare to 50 healthy controls were included in this study. Isolation and identification of uropathogenic bacteria , and use enzyme-linked immunosorbent assays to check serum levels of interleukin-34 and interleukin-35.The results revealed that *E. coli* accounted for 70% of the uropathogenic bacteria identified, with *Proteus* spp. come in second accounted 20% followed by *Klebsiella* spp. accounted 6%., while *Enterococcus fecalis* and *Enterobacter* spp. accounted for 2% with each. A notable rise in serum levels of IL-34 and IL-35 was observed when comparing patients with systemic lupus erythematosus illness to controls, with a *P*.value of less than 0.05.This study investigated that *E. coli* was the most frequently occurring of uropathogenic bacteria and showed higher serum levels of interleukin IL-34 and IL-35 in women with systemic lupus erythematosus.

Keywords: Urinary tract infection,IL-35,IL-34,SLE,Uropathogenic bacteria

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1.Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that happens when autoantibodies cross react with nuclear antigens, Antigen-Antibody immune complex deposit, lead to damage in the kidneys, skin, heart and lung (1). Among women of reproductive age, SLE is more common. There are a number of variables that put women at increased risk of developing SLE, including disease symptoms, multiple heterophils antibody production by B cells, and autoreactive T cell activation, which can be caused by a combination of hereditary and environmental factors, as well as disruptions adaptive and innate immune systems which consider the important parts of immune system(2,3).Systemic lupus erythematosus may lead to a variety of problems, including urinary tract infections (UTIs) and lupus nephritis. Before diagnosing SLE, lupus cystitis may manifest as vague or nonexistent symptoms in the urinary tract. It's still not clear what the best way is to treat UTIs in people with SLE, but histopathological studies have shown that immune complex-mediated mechanisms play a big role. Lupus cystitis is an uncommon form of SLE, but doctors are having a difficult time diagnosing it because of how tough it is (4,5). The part that interleukin-34 (IL-34) plays in changing the biology of mononuclear phagocytic cells was first found when it was found to be a substitute for the colony-stimulating factor-1 receptor(6,7,8). The significant role of IL-34 was differentiation and proliferation of mononuclear phagocyte cells, osteoclastogenesis, progression of Langerhans cells and microglia, and inflammation (9,10) .Interleukin-35, a member of the IL-12 family, is a biomarker that T-regulatory cells generate. It is used as a therapeutic tool, and it may be used as a diagnostic tool in the treatment of autoimmune and cancer disorders, as well as SLE disease (11,12).

2.Materials and Methods

This study was case control study conducted from March 2023 to June 2024, included65 women with SLE were admitted to the Consultant Clinic at the Department of Rheumatology, Baghdad Teaching Hospital. Their condition was diagnosed using the Systemic Lupus International Collaborating Clinics index of the American College of Rheumatology(13) . The patients' ages varied from 18 to 65 years old . Fifty healthy women served as a control group, and the SLE patients were compared to them.

Blood and urine were the two specimens taken. Before specimen collection, subjects were asked to wash their outside genitalia with water and to gather midstream urine into a sterile wide-mouth container, after that done general urine examination then culturing done by taken a loopful of urine (0.01 ml) and streaking on the blood and MacConkey culture media . Finally, the diagnosis was verified by Vitek 2 Impact after biochemical testing identified the isolates. The blood samples were separated to serum. We assessed the interleukin-34 and interleukin-35 serum levels in patients and controls using the quantitative sandwich enzyme immunoassay (ELISA) method.

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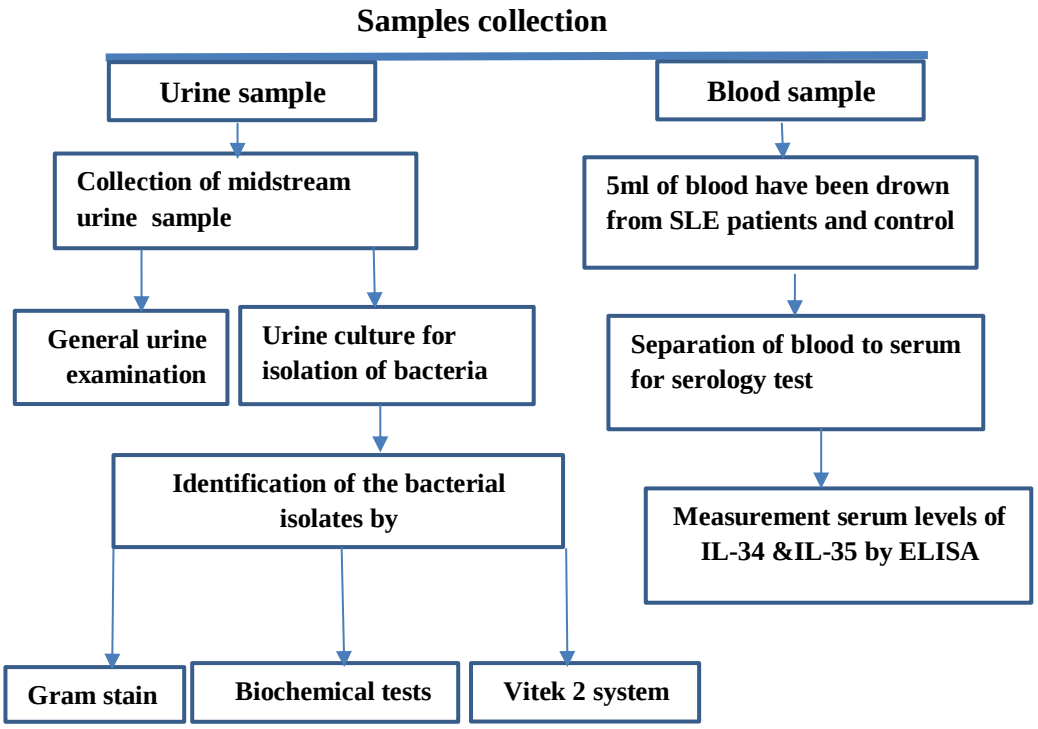
We entered the data into a database system for statistical analysis. We used SPSS version 17 (Statistical Package for the Social Sciences).



Scheme 1:The current study design

3.Results

According to the study, Table 1 revealed that SLE most frequently affects women between the ages of 20 and 39.

Table 1:Age distribution in patients with SLE disease

Age\years	Patients with SLE		Healthy control	
	No.	%	No.	%
<20	2	3.2 %	4	8%
20—29	27	41.5%	16	32%
30—39	24	36.9 %	22	44 %

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40—49	8	12.3%	5	10%
50—59	3	4.6%	2	4 %
=>60	1	1.5%	1	2%
Total	65	100%	50	100%

Table 2 showed that out of 65 female patients with SLE , 50 (76.9%) had a UTI, while 15 (23.1%) SLE patients who did not experience a UTI.

Table 2: Percentage frequency of urinary tract infection in SLE patients

Patients with SLE	UTI			
	UTI +ve		UTI –ve	
	No.	%	No.	%
65	50	76.9%	15	23.1%

Bacteria caused urinary tract infections in the SLE patients under study. The proportion frequency for *Proteus* spp. was 20 %, whereas *E. coli* was represented at 70%. Just 6% of the sample included *Klebsiella* spp., *E.fecalis*, and *Enterobacter* spp., according to table 2, accounted 2%.

Table 3: Laboratory finding of UTI in patients with SLE disease

	Bacteria spp. N=50	**No. of bacterial isolates**	**No. %**
1	*E.coli*	35	70%
2	*Proteus spp.*	10	20%
3	*Klebsiella spp.*	3	6%
4	*Enterococcus fecalis*	1	2%
5	*Enterobacter spp.*	1	2%
	Total	**50**	**100%**

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The serum level of IL-34 in the women with SLE was noticeably greater than in the healthy controls ($p < 0.001$), as shown in Table 4.

Table4: Serum level of IL-34 in patients with SLE disease and controls

IL-34 (pg/ml)	SLE Patients (n=65)	Controls (n=50)	*P* value
Range	27.2-110.5	0.5-24.6	0.001*
Mean±SE	63.05±24.43	10.3±3.2	
Median	18.2	5.3	

Serum IL-35 levels were also significantly different between the healthy control group and the SLE patients women (Table 5).

Table 5: Serum level of IL-35 in patients with SLE disease and controls.

IL-35(pg/ml)	SLE Patients (n=65)	Controls (n=50)	*P* value
Range	28–88	10.5–36.8	0.001*
Mean±SE	53.64±16.07	22.37±7.54	
Median	51	22.2	

Regard table 6 the Sensitivity , Specificity and Accuracy of IL-34 represented (91.5 %, 95.1%,92.6%) respectively and cut-off value was 4.48, while Sensitivity ,Specificity and Accuracy o of IL-35account (89.5%,92.4%,89.5%) respectively and cut-off value was 8.78

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Table 6 : Sensitivity, Specificity and accuracy of IL-34 and IL- 35

Tested IL	cut-off value	Sensitivity	specificity	ppv	NPV	Accuracy
IL-34	4.48	91.5 %	95.1%	85.3%	88.4%	92.6%
IL-35	8.78	89.5%	92.4%	82.4%	84.4%	89.5%

4.Discussion

Systemic lupus erythematosus may affect anybody at any age or from any ethnic background, although over 90% of newly diagnosed cases are in women of childbearing age. The research found that SLE is more common in women between the ages of 20 and 39, and it may occur in individuals ranging from 20 to 60 years old.

When a woman experiences the initial, often subtle, symptoms of a disease, which are often linked with a rapid diagnosis, this is the age at which SLE typically begins to manifest. The symptoms might manifest at any point in a woman's life, whether it's in her youth, middle age, or old age.

The prognosis differs according to the age at which the symptoms first appear; a poor prognosis is associated with SLE illness when it first manifests in childhood (14). Recent discoveries of multiple investigations and clinical confirmations explain the significant involvement of infections in the development or worsening of autoimmune illness (15). Infectious pathogens may contribute to the development of autoimmune diseases, which explains the molecular mimicry process. The immune system would target both alien and self-tissues when they had structural similarities (16). Given that many women experience urinary tract infections, it is reasonable to assume that UTIs play a role in systemic autoimmunity (17). In the present investigation, the most common bacterial isolates found in UTI+ve SLE patients were *E. coli* (70%), *Proteus* spp. (20%),followed by *Klebsiella pneumoniae accounted* 6% , *Enterococcus fecalis*, and *Enterobacter* spp. each was 2% ,These results may also shed light on the role that these bacteria and UTI play a role in the development of SLE (18,19). The urinary tract infection was also identified in research by Hidalgo-Tenorio *et al.* (2004)that included SLE patients.

These patients tended to have *E. coli* infections that had spread across the community(20). The results can be explained by the fact that the infectious agent was Gram-negative bacteria, as a result, molecular mimicry can be proposed as a mechanism of pathogenesis in SLE patients. In order to further understand the association between SLE and UTIs caused by different pathogens, more experimental studies, preferably based on animal models, are definitely needed (21). The immune system relies on inflammatory mediators, which transmit signals between immune cells, to carry out its functions (22). This is why inflammatory cells in SLE secrete inflammatory interleukins, which further exacerbate the inflammation. Disease progression is associated with alterations in interleukin levels. in order to study the expression

of our target cytokines in SLE patients, we compared the serum levels of IL34 and IL35 in female patients with SLE to those in the control group. Tables 4 and 5 reveal that IL-34 and IL-35 levels were much greater in the SLE group than in the control group, according to the present study's results

Consistent with previous research showing extremely significant variations in IL-34 between SLE patients and control groups, the present study confirms the findings of Wang *et al*. (2016) and El-Gawish *et al*. (2019) in Egypt.IL-34 in renal illness and SLE . There was a favorable correlation between IL-34 serum levels in individuals with SLE (24). Lupus nephritis, an inflammatory kidney disease characterized by SLE that is associated with high rates of morbidity and death, has emerged as an independent risk factor for IL-34 (25,26). Both B-regulatory cells and T-regulatory cells are capable of producing IL-35. The up- or downregulation of both T-regulatory and B-regulatory might therefore influence serum IL-35 levels. The little elevation of IL-35 levels seen in SLE patients might be explained by this (27, 28).

Based on these findings, IL34 and IL35 may be potential therapeutic targets for SLE, as they are valuable prognostic indicators in SLE and are implicated in SLE formation and disease progression.

Interleukin-34 and IL-35 showed high diagnostic predictor for SLE with Sensitivity , Specificity and Accuracy of IL-34 account (91.5 %, 95.1%,92.6%) respectively and cut-off value was (4.48), while Sensitivity ,Specificity and Accuracy o of IL-35 account (89.5%,92.4%,89.5%) respectively and cut-off value was (8.78).

5.Conclusion

Urinary tract infection was a significant clinical consequence of systemic autoimmunity, and IL-35 and IL-34 contribute to the pathogenesis either alone or in combination with other cytokines. Due to their multi-faceted pathogenic consequences, these cytokines have promise as predictor diagnostic indicators and therapeutic targets for SLE patients women with UTIs.

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