Egyptian Journal of Medical Microbiology Volume 34 / No.3 / July 2025 25-32 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Interferon-Induced Protein-10 and Plasma Interleukin-26 in Systemic Lupus Erythematosus

[1]Asmaa S. Hegab, [1]Nancy N. Abd Allah, [1]Lamiaa A.F. Mdkour, [1]Magda I. Ayoub, [2]Ahmed A. El-Maghraby, [1]Hanaa F. Abdel Aty*

[1]Medical Microbiology and Immunology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2]Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Key words:
Interleukin 26, Interferon-induced protein 10, Systemic lupus erythematosus

Corresponding Author:
Hanaa F. Abdel Aty
Medical Microbiology and Immunology Department, Kasr-Alainy Faculty of Medicine, Cairo University, Cairo, Egypt
Tel.: 011125044080
hfathy2@kasralainy.edu.eg

ABSTRACT

Background: *Systemic lupus erythematosus is a chronic, immune-mediated, multifactorial illness that affects multiple systems. One cytokine that has a role in the pathophysiology of a number of inflammatory diseases is interferon-induced protein 10 (IP-10). The newest member of the IL-20 cytokine subfamily, interleukin-26 (IL-26), is a novel mediator of inflammation that is overexpressed in activated immune cells.* ***Objective:*** *The aim of this work was to assess the plasma levels of IL-26 and IP-10 expression in peripheral blood mononuclear cells (PBMCs) in lupus patients and healthy controls, as well as establishing a relationship between these levels and lupus activity.* ***Methodology:*** *Forty-five lupus patients with forty-five matched controls were included. The real-time reverse transcription-polymerase chain reaction (RT-PCR) was used to evaluate IP-10 expression levels in PBMCs, while plasma IL-26 levels were measured using the enzyme-linked immunosorbent assay (ELISA).* ***Results:*** *Compared to the control group, lupus patients had significantly higher levels of plasma IL-26 and PBMC expression of IP-10 (P-value < 0.001). The levels of IP-10 expression and lupus activity were shown to be significantly positively correlated (r = 0.361, P-value < 0.015). Furthermore, a significant relationship between lupus activity and IL-26 levels was observed (r = 0.573, P-value < 0.001). The levels of IL-26 and IP-10, meanwhile, showed a strong positive correlation (r = 0.619, P < 0.001).* ***Conclusion:*** *IP-10 and IL-26 might be useful biomarkers for lupus diagnosis and prognosis, as well as promising therapeutic targets.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune illness that impacts several systems in the body and follows a pattern of remissions and exacerbations. The actual reason of SLE is not well recognized, but it is known that immune responses are triggered by interaction between genetic and environmental factors. These responses lead to the overproduction of autoantibodies and cytokines, causing harm to organs and tissues. Antibodies that target antigens of the nucleus and cytoplasm are a defining feature of SLE [1].

Interferon-induced protein 10 (IP-10) is produced by various cell types, including T-lymphocytes, neutrophils, monocytes, endothelial cells, and fibroblasts[2]. IP-10 acts as a chemotactic agent for activated T helper 1 (Th1) lymphocytes and, in conjunction with IL-6, promotes differentiation of plasma cells. An amplifying feedback loop may be created when the recruited Th1 lymphocytes help to promote the production of gamma interferon (IFN-γ), which in turn encourages more IP-10 synthesis from other cells. The significance of these substances is highlighted by the increased levels of IFN-γ detected in SLE patients [3].

On the other hand, interleukin 26 (IL-26), a proinflammatory member of the IL-10 family, is primarily produced by T helper 17 (Th17) lymphocytes [4]. It has a major impact on a number of inflammatory illnesses with both infectious and autoimmune causes. Notably, IL-26 has the unique ability to directly destroy extracellular bacteria via hole formation and to participate in toll-like receptor-9 (TLR9) mediated DNA sensing [2]. Consequently, IL-26 acts as a "double-edged sword" in the immune system, contributing to tissue damage brought on by inflammation while simultaneously supporting antimicrobial defense[5].

In this context, previous studies have provided increasing evidence that IP-10 expression in lupus lesions plays a significant role and is closely correlated with illness activity. Nonetheless, the precise function of IP-10 in lupus pathogenesis is yet unknown [6]. Additionally, IL-26 has also been shown to be essential to the pathogenesis of lupus[5]. Comparing the expression levels of IP-10 in PBMCs and IL-26 plasma levels in lupus patients with those in healthy controls, as well as

establishing a correlation between the levels of these markers and lupus activity, were the objectives of the current study.

METHODOLOGY

This observational cross-sectional study included 45 SLE patients and age- and gender-matched healthy subjects. The 45 cases with SLE were either coming to the Rheumatology and Rehabilitation Department's Outpatient Clinic or admitted to the Inpatient Unit, Cairo University Hospitals, over the course of a year, from January 2023 to January 2024. The research was performed with adherence to the Helsinki Declaration, and the protocol obtained clearance from the Institutional Review Board's Research Ethics Committee (approval number: MD-413-2022), Faculty of Medicine, Cairo University. Before study beginning, participants gave their informed consent.

Data concerning the patient's demographics, clinical aspects, and laboratory findings were recorded. Nephritic individuals underwent renal biopsies. The enrolled patients met the classification requirements set forth by the Systemic Lupus International Collaborating Clinics (SLICC) [7]. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to measure illness activity, and patients were clinically categorized into three groups: mild (quiescent; SLEDAI 1-5), moderate (moderately active; SLEDAI 6–10), and severe (severely active; SLEDAI > 10)[8].

Every participant had a clean venipuncture performed under aseptic settings to withdraw five milliliters of peripheral venous blood gathered in a tube with ethylenediamine tetra acetic acid (EDTA). For each specimen, a density-gradient medium (Ficoll-Hypaque) was added, then centrifuged at 3000 revolutions per minute (rpm) for 30 minutes to separate PBMCs and plasma for each sample. PBMCs were collected by pipetting and kept at −80°C for subsequent investigation of IP-10 expression using quantitative reverse transcription PCR (qRT-PCR) at the Molecular Biology Unit of the Medical Biochemistry Department, Faculty of Medicine, Cairo University. The plasma aliquot was kept at −20°C at the Medical Microbiology and Immunology Department, Faculty of Medicine, Cairo University, for quntitative detection of IL-26 levels using Human IL-26 ELISA Kit (RayBio® Human IL-26 ELISA Kit, USA) following the manufacturer's instructions.

Detection of IP- 10 expression levels: After extraction of the total RNA from PBMC specimens using miRNeasy Micro kit (Qiagen, Valencia, CA, USA), reverse transcription was performed using the Applied Biosystems™ High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, USA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a housekeeping gene, was used to quantify the relative expression of IP-10. The target cDNA and the housekeeping gene were amplified using Maxima SYBR Green/ROX qPCR Master Mix (2X) in accordance with the manufacturer's instructions (Thermo Scientific, USA). Table 1 displays the IP-10 sequence-specific primers. Using the ΔCt technique, the expression level of IP-10 was assessed. To determine the fold change in IP-10, $2^{-\Delta\Delta Ct}$ for relative expression was used.

Table 1. Primer sequences of the target gene (IP-10) and GAPDH

Gene	Primer sequence *
IP-10	Forward primer-5'-GAAATTATTCCTGCAAGCCAATTT-3'
	Reverse primer-5'-TCACCCTTCTTTTTCATTGTAGCA-3'
GAPDH	Forward primer-5'-TGGCATTGTGGAAGGGCTCA-3'
	Reverse primer-5'TGGATGCAGGGATGATGTTCT-3'

*National Center for Biotechnology Information by Primerdesign Biotechnology Company.

Statistical analysis:

Data entry and coding were done using IBM Corp.'s statistical program for the social sciences (SPSS) version 28 (Armonk, NY, USA). Mean, standard deviation, median, minimum, and maximum were employed to represent quantitative data, while frequency (count) and relative frequency (%) were used to describe categorical data. The Spearman correlation coefficient in Mann-Whitney tests was used to look at correlations between quantitative variables, and non-parametric Kruskal-Wallis and regression analysis were used to compare quantitative data. An area under curve analysis was utilized to create a receiver operating characteristic (ROC) curve in order to ascertain the ideal cutoff value of markers for case detection. For statistical significance, a *P-value* of less than 0.05 was considered[9].

RESULTS

All participants were female (100%), with patients aged 14-45 years (mean, 32.51 ±8.89) and controls aged 13-48 years (mean, 30.45 ±9.69) (*P- value* = 0.109). Within the 45 SLE individuals, the most prevalent symptoms were those of arthritis (77.8%), followed by nephritis (68.9%) and cutaneous manifestations

(66.7%). The ANA was the most frequent laboratory biomarker (93.5%), followed by anti- DNA (57.8%) and proteinuria and pyuria (40%). Steroids were the most frequently administered drugs (100%), followed by hydroxychloroquine (71.1%) and azathioprine (66.7%). According to the SLEDAI scoring system, 16 individuals (35.6%) exhibited mild lupus, 17 individuals (37.8%) had moderate lupus, and 12 individuals (26%) displayed severe lupus (Table 2).

Table 2. Characteristics of systemic lupus erythematosus patients

Parameters	Cases	
	Count	%
Clinical feature		
Arthritis	35	77.8
Nephritis	31	68.9
Cutaneous manifestations	30	66.7
Oral ulcers	17	37.8
Serositis	17	37.8
Neurological manifestations	16	35.6
Vasculitis	15	33.3
Photosensitivity	14	31.1
Laboratory findings		
ANA	42	93.3
Anti-DNA	26	57.8
Proteinuria	18	40.0
Pyuria	18	40.0
Hematuria	10	22.2
Treatment options		
Steroid	45	100
Hydroxychloroquine	32	71.1
Azathioprine	30	66.7
Renal Biopsy (class)		
2*	2	6.5
3**	16	51.6
4***	13	41.9
SLEDAI scoring system		
Mild	16	35.6
Moderate	17	37.8
Sever	12	26

* Mesangial proliferative glomerulonephritis, ** Focal glomerulonephritis, *** Diffuse proliferative nephritis

The patients' IL-26 plasma levels were highly significant (range, 16.70-137.80 pg/ml; median, 50.20 pg/ml), while in the control group, the levels ranged from <3.3-22.9 pg/ml (median, 5.02 pg/ml) (*P- value* <0.001). The IP-10 protein expression was significantly high in SLE cases (range, 2.03-12.25; median, 6.16) compared to controls (range, 0.87-7.88; median, 1.22) (*P- value* < 0.001).

There was a significant association between elevated IP-10 protein expression levels and lupus neurological manifestations, as evidenced by a significant difference (*P- value* = 0.016), lupus nephritis manifested by pyuria (*P- value* = 0.037), and hematuria (*P- value* = 0.014) (figure 1).

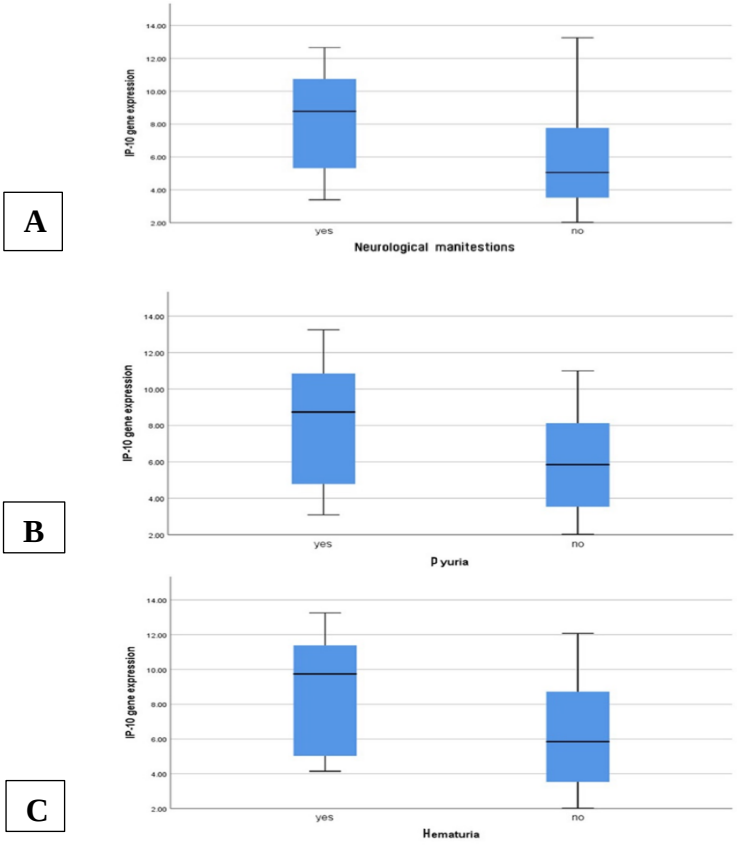

Fig. 1. Relation between IP-10 expression and A) the existence or non-existence of neurological manifestations, B) The existence or non-existence of pyuria, C) The existence and non-existence of hematuria

Elevated IL-26 plasma levels were significantly associated with lupus nephritis manifested by pyuria (*P- value* = 0.035) and hematuria (*P- value* = 0.001) (Figure 2).

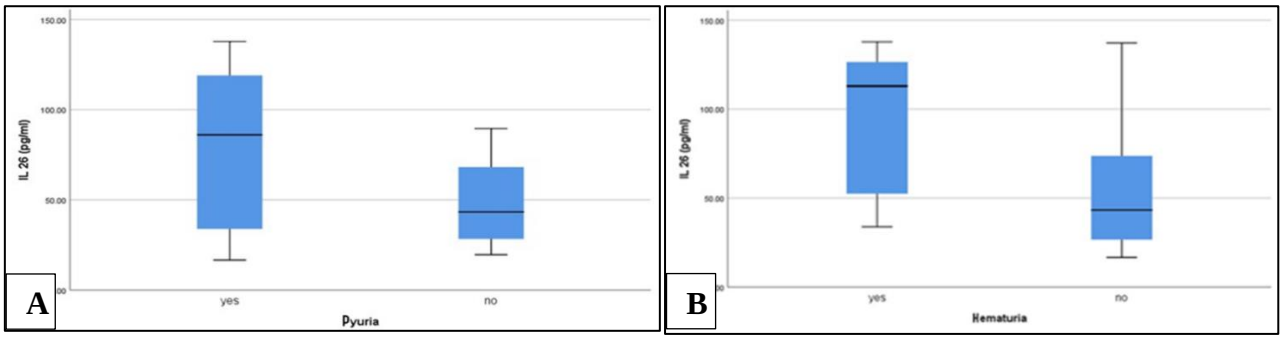

Fig. 2: Relation between IL-26 plasma level and A) The existence or non-existence of pyuria, B) The existence and non-existence of hematuria

The current study revealed a direct proportionality between IP-10 expression and the activity of lupus assessed by SLEDAI score (r = 0.361 and *P- value* <0.015) as well as between IL-26 and the activity of lupus measured by SLEDAI score (Figure 3).

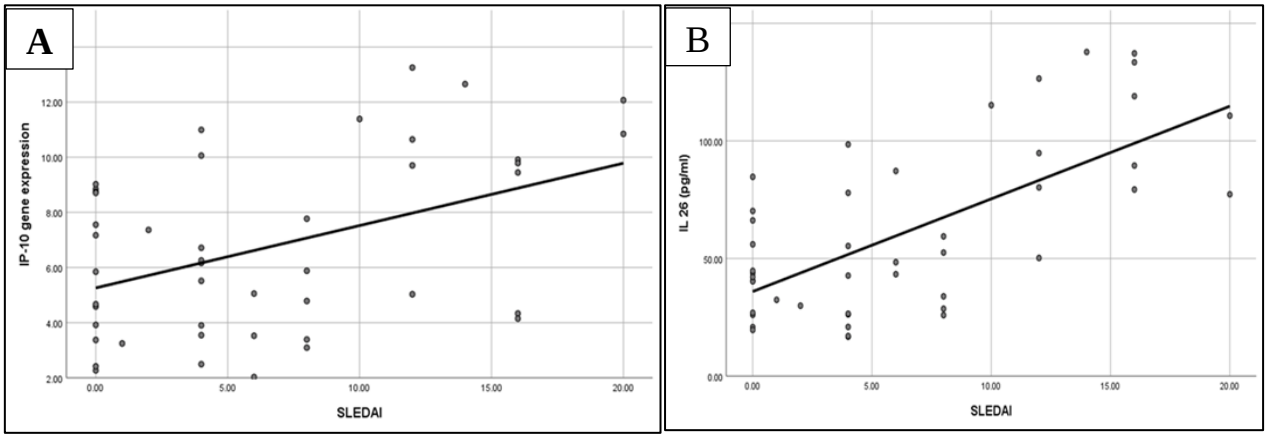

Fig. 3 : Scatterplot curve showing A) a positive correlation between IP-10 protein expression and SLEDAI score (r = 0.361, P < 0.015), B) a positive correlation between IL-26 plasma levels and SLEDAI score (r=0.573, P < 0.001), P: P-value; r: correlation coefficient

The analysis showed a direct proportionality between IP-10 expression levels and IL-26 plasma levels (r = 0.619, *P-value* < 0.001) among individuals within the case group. This correlation signified a statistically positive relationship between the two variables (Figure 4).

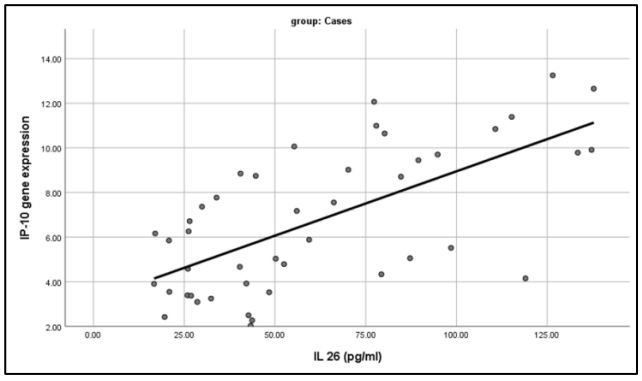

Fig. 4. Scatterplot curve showing the correlation between IP-10 protein expression and plasma IL-26 (r=0.619, P<0.001). P: P-value; r–correlation coefficient

At a cutoff value of 1.8594 fold change, IP-10 expression levels were found to be an effective means of distinguishing between lupus patients and healthy controls using receiver operating characteristic (ROC) curve analysis. There was a significant *P-value* < 0.001 with a sensitivity of 98.5% and specificity of 84.1%. When IL-26 plasma levels were assessed using the ROC curve, it was discovered that, at a cutoff value of 24.4 fold change, IL-26 plasma levels showed the ability to discriminate between people with lupus and healthy people. 98% was the specificity and 88.9% was the sensitivity. These results produced a *P-value* of 0.001, which is statistically significant (Figure 5).

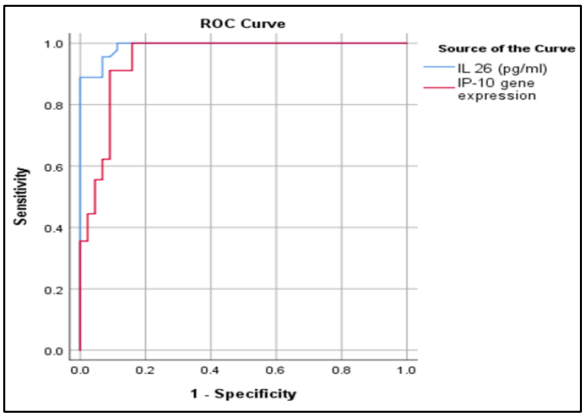

Fig. 5: ROC curve showing sensitivity and specificity of IP-10 expression levels and plasma IL-26

DISCUSSION

Systemic lupus erythematosus is an autoimmune condition distinguished by the existence of autoantibodies and the formation of immune complexes that damage tissues[10]. IP-10, also referred to as chemokine ligand 10 (CXCL10), is an IFN-regulated cytokine with a strong link to SLE disease activity. In reaction to IFN activation, endothelial cells, monocytes, and macrophages release it[11]. One cytokine that is associated with the IL-10 family is IL-26. Activated T lymphocytes, especially Th17 cells, and NK cells both express IL-26 mRNA. Patients with chronic inflammatory diseases have higher serum levels of IL-26[12]. Reports state that IL-26 interacts with DNA to trigger the release of IFN-I by plasmacytoid dendritic cells (pDCs) through TLR9 [13].

The present study was designed to compare the expression levels of IP-10 in PBMCs and IL-26 plasma levels in lupus patients with those in healthy controls, as well as to correlate between the expressions levels of IP-10, IL-26 plasma levels, and lupus activity.

In the current study, all subjects in both case and control groups were females. While other studies[10,14] reported that the percentage of female participants was approximately twice that of male participants. This difference may be attributed to factors such as X-chromosome involvement and hormonal changes, which may contribute to a higher prevalence in females.

In this work, lupus patients presented mainly with arthritis (77.8%), nephritis (68.9%), and mucocutaneous manifestations (66.7%). On the other hand, a previous study revealed that lupus patients presented mainly with nephritis (42.9%), alopecia (42.9%) and fever (40%)[10].

In our study, lupus patients had elevated laboratory findings, including ANA (93.3%), anti-DNA (57.8%), proteinuria, and pyuria (40%). Likewise, in Khalil et al.'s study [10], the patients' laboratory findings showed mainly ANA (98.9%), anti- DNA (62.8%), and hematuria (47%). Choi et al. [15] showed that 93.8% of SLE patients were ANA positive. On the other hand, Moness et al. [16] and Aringer et al.[17] clarified that 100% of patients with SLE were positive for ANA. Brilland et al. [14] found that anti-DNA antibodies were elevated within 40-70% of SLE patients.

In the current study, lupus activity among the case group was assessed using the SLEDAI index. Among this group, 16 subjects (35.6%) showed mild lupus, 17 subjects (37.8%) had moderate lupus, and 12 subjects (26%) exhibited severe lupus. According to Khalil et al. [10], 31% classified as mild, 23.1% as moderate, and 45.2% as high. This higher percentage of severe lupus may be because Khalil et al. [10] study group consisted of both females and males, while our study consisted of females only.

Regarding the treatment regimen, all participants in the case group received steroids (100%), with hydroxychloroquine administered to 71.1% of them, followed by azathioprine to 66.7%. In the study [10], steroids were also used universally (100%), followed by azathioprine at 28.6%. However, they differed from our study in employing mycophenolate mofetil (26%) instead of hydroxychloroquine. In Moness et al.'s study[16], 91.1% of active lupus patients were receiving steroid and hydroxychloroquine plus immunosuppressive treatment and 8.9 % of patients were receiving steroid and hydroxychloroquine or hydroxychloroquine only

In this investigation, IP-10 expression level in PBMCs was significantly higher in lupus patients (mean ± SD = 6.71±3.17) compared to the control group (mean ± SD = 1.76±1.57) (*P- value* <0.001). This finding aligns with that of Torres-Vázquez et al.[18]. Similarly, Welcher et al.[19] employed ELISA and documented that IP-10 levels in lupus blood samples were higher than those in healthy samples. Additionally, Rose et al. [20] utilized flow cytometer and reported that IP-10 levels in lupus samples were four times higher than those in normal blood samples. Conversely, Lu et al. [21] investigated IP-10 expression in the lymph nodes of lupus nephritis patients and noted a significant decrease in IP-10 expression compared to that in healthy controls. This variation could be elucidated by the fact that lupus patients in their study were treated with an anti- tumor necrosis factor like weak inducer of apoptosis (anti-TWEAK) antibody.

Meanwhile, this study revealed no significant correlation between the IP-10 gene expression and age (*P*-value = 0.061) within the case group. These results agreed with those of earlier research [18, 21].

However, our research found a strong correlation between increased IP-10 expression and both lupus nephritis and lupus neurological symptoms. The activity of the disease, especially lupus arthritis, was found to be correlated with IP-10 levels, according to Espinosa-Bautista [22]. In contrast, Kong et al. [23] observed that there was no appreciable variation in blood IP-10 levels between patients with and without renal or central nervous system symptoms, possibly due to the small number of patients exhibiting these manifestations.

According to this study, there is a direct relation between IP-10 gene expression and lupus activity (r = -0.361, *P-value* < 0.015). Other investigations reported similar findings[18, 20, 24]. Furthermore, serum IP-10 may be a potential serologic biomarker representing the activity of sickness and renal affection in individuals with SLE, according to research by Choe & Kim[25]. Furthermore, IP-10 in serum and urine were shown to be potentially helpful indicators of lupus activity by Abujam et al.[26]. However, El-Gohary et al. [27] discovered that the albumin/creatinine ratio was better at detecting lupus nephritis and renal activity, while IP-10 in serum and urine was a significant indication of lupus activity but did not reflect renal activity.

Regarding IL-26 plasma level, it was found to be elevated in lupus patients (mean ± SD = 61.24 ± 36.07) compared to healthy controls (mean ± SD = 6.20 ± 5.45), with a significant statistical difference (*P-value* < 0.001). Other earlier investigations revealed similar results [10, 14]. Furthermore, Ouyang et al. [28] highlighted the importance of the IL-10 family (including IL-26) in SLE pathogenesis.

Within the case group of the current investigation, there was no significant correlation between age and IL-26 plasma levels (*P-value* = 0.411). Other studies reported the same finding [10, 14].

In the current investigation, SLE individuals demonstrated that IL-26 was significantly related to pyuria and hematuria, as two manifestations of lupus nephritis. Similarly, other studies displayed that IL-26 was significantly related to proteinuria, as an indication of renal damage [10, 14].

This study displayed a notable directly proportional relationship between IL-26 and lupus activity (r = 0.573, *P-value* < 0.001). Similar findings were documented by other previous studies [10, 14].

Of note, there was a significant directly proportional relationship in the present study between IP-10 expression and IL-26 plasma level (*r = 0.619, P- value* < 0.001) in SLE patients.

Meanwhile, IP-10 gene expression in this study exhibited 98.5% sensitivity and 84.1% specificity for detecting SLE. Abujam et al.[26] demonstrated similar results, with 93% sensitivity and 89% specificity. Additionally. Zhang et al.[29] discovered that IP-10 had higher sensitivity and specificity than standard laboratory values differentiating between quiescent and active lupus. Moreover, Odler et al.[30] illustrated that IP-10 in serum served as a valuable indicator for detecting lung affection in SLE, with 66.67% sensitivity and 100% specificity. In contrast, Torres-Vázquez et al.[18] reported that the evaluation of IP-10 gene expression yielded suboptimal results, with a sensitivity of 50% and specificity of 75%, indicating the necessity for further investigations to enhance SLE diagnosis.

In this study, it was found that IL-26 had an 88.9% sensitivity and a 98% specificity for detecting SLE. According to Khalil et al.[10], IL-26 had 90.5% sensitivity and 100% specificity. Brilland et al. [14] also revealed a substantial association between IL-26 levels and SLEDAI score, with sensitivity of 100% and specificity of 89% for identifying active SLE.

This study has some limitations, including the relatively small sample size as well as the involvement of female patients only that may limit the generalizability of the findings to the broader population of SLE patients.

CONCLUSION

Our findings support the participation of the immune system and interferon pathway in the systemic inflammation associated with lupus. IP-10 and IL-26 demonstrated a potential to be sensitive and specific biomarkers for activity detection in SLE patients. Both were helpful in diagnosing SLE in conjunction with other diagnostic criteria, and they can be relied upon for that purpose. Nonetheless, further data are needed to confirm their role in systemic inflammation and comorbidities of lupus.

Declarations;

Ethics approval and consent to participate: The protocol obtained clearance from the Institutional Review Board's Research Ethics Committee (approval number: MD-413-2022), Faculty of Medicine, Cairo University. Before the study began, patients gave their informed consent.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest: The authors declare no conflict of interest.

Funding: The study was part of the MD thesis of Dr. Nancy N. Abd Allah, Medical Microbiology and Immunology, Faculty of Medicine, Cairo University. The authors express their appreciation to Cairo University for providing the fund.

Acknowledgements: Not applicable

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