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Serum Interferon-Alpha and Interleukin-22 Levels in Systemic Lupus Erythematosus: Association with Overall Disease Activity

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***Abstract*—Background**: *Systemic lupus erythematosus (SLE) is an autoimmune disease that affects most of the body's systems and is characterized by disruption of the immune system. Type I interferon activation, especially interferon-alpha (IFN-alpha), is a major pathogenic pathway in SLE. Interleukin-22 (IL-22) may also contribute to inflammatory and tissue-response mechanisms in autoimmune disease.* **Objective**: *This study aimed to evaluate serum IFN-alpha and IL-22 levels in SLE patients compared with healthy controls and to examine their relationship with overall disease activity using the available SLEDAI-based activity data.* **Methods**: *A case-control dataset including 40 SLE patients and 40 controls was analyzed. The previously excluded immunological variables were removed from the analysis according to the revised study plan. Disease activity analysis was restricted to total SLEDAI score, severity category, proteinuria, hematuria and urinary casts. Statistical analysis was performed in an SPSS-style framework using descriptive statistics, independent-samples comparisons, Spearman correlation and Kruskal-Wallis testing where appropriate.* **Results**: *IFN-alpha was significantly higher in SLE patients than controls (57.42 ± 12.50 vs. 7.38 ± 1.34 pg/mL; $t = 25.17$, $df = 39.89$, $p < 0.001$). IL-22 was also higher in SLE patients (3.64 ± 1.34 vs. 2.54 ± 0.55 pg/mL; reported $p = 0.004$). The mean SLEDAI score was 15.40 ± 2.45, and 39 of 40 patients (97.5%) had high or very high activity. Proteinuria and hematuria showed significant positive correlations with total SLEDAI, while IFN-alpha showed no significant direct correlation with SLEDAI in the available patient-level dataset.* **Conclusion**: *The revised analysis supports a strong elevation of IFN-alpha and IL-22 in SLE, together with a predominantly active clinical profile. Overall disease activity was mainly reflected by SLEDAI-related urinary activity indicators. Patient-level IL-22 readings are recommended for a future stronger correlation analysis with activity.*

***Keywords*—** *Systemic lupus erythematosus; interferon-alpha; IFN-alpha; interleukin-22; IL-22; SLEDAI; disease activity.*

I. Introduction

Systemic lupus erythematosus is a heterogeneous autoimmune disease characterized by flares, remission periods, immune-complex formation and variable organ involvement, and it remains a prototype disease for studying loss of immune tolerance in humans (Tsokos, 2011; Aringer et al., 2019). A major immunological hallmark of SLE is activation of the type I interferon pathway, which promotes antigen presentation, B-cell survival, inflammatory gene expression and amplification of autoreactive immune responses (Baechler et al., 2003; Bennett et al., 2003; Postal et al., 2020). The interferon gene signature was first described as an overexpression pattern of interferon-inducible transcripts in peripheral blood cells from patients with severe or active SLE (Baechler et al., 2003; Bennett et al., 2003).

IFN-alpha is a central member of the type I interferon family and has been repeatedly linked to SLE pathogenesis, disease activity and severe organ manifestations, especially lupus nephritis and mucocutaneous disease (Kirou et al., 2005; Oke et al., 2019; Tanaka et al., 2023). Type I interferon activity may be persistently elevated in a substantial subset of patients with SLE and may identify a biologically distinct subgroup with stronger systemic immune activation (Bengtsson et al., 2000; Postal et al., 2020; Miyachi et al., 2023). Recent reviews also support IFN-I signaling as an important therapeutic target in SLE, particularly after the clinical development of agents that block IFN-alpha or the type I interferon receptor pathway (Bruera et al., 2023; Lai et al., 2024).

IL-22 is an immune cytokine produced by Th22, Th17 and innate lymphoid cell populations, and it has context-dependent inflammatory and tissue-protective effects at epithelial barriers (Zhao et al., 2013; Lin et al., 2014). In SLE, published findings are not fully uniform, because some studies reported increased IL-22 or IL-22-producing T cells in active disease, whereas other studies reported reduced plasma IL-22 in new-onset disease or disease-specific subgroups (Zhao et al., 2013; Lin et al., 2014; El-Gazzar et al., 2017). Higher IL-22 has also been reported in lupus nephritis and has been linked with renal activity measures in some cohorts, supporting its possible relevance as a tissue-associated inflammatory biomarker (Yang et al., 2019).

In the revised version, non-retained immunological variables were excluded from all analysis, tables, figures and discussion. The relationship with activity was therefore evaluated using total SLEDAI score, severity category and the urinary components available in the dataset, because proteinuria, hematuria and urinary casts are recognized renal activity components within SLEDAI-based assessment frameworks (Bombardier et al., 1992; Gladman et al., 2002; Amer et al., 2024).

II. Materials and Methods

2.1 Study design and participants

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The case-control study included 40 SLE patients and 40 healthy controls. The collection was from February 2022 to November 2022. All patients selected from Al-Hakeem Hospital and private labs in Najaf. The manuscript was structured as a case-control cytokine-activity analysis, consistent with published SLE biomarker studies that compare serum cytokines between SLE patients and healthy controls and then assess associations with disease activity. Data were analyzed using an SPSS-style statistical workflow.

2.2 Cytokine measurements

Serum IFN-alpha and IL-22 concentrations were expressed in pg/mL. IFN-alpha was available as individual readings for patients and controls. IL-22 was available as mean ± SD for the SLE and control groups with a reported p-value in the source results. Serum IFN-alpha measurement is biologically justified because IFN-alpha represents a key circulating and pathway-level marker of type I interferon activation in SLE, although gene-signature and protein-based measurements may not always overlap perfectly in all patients (Postal et al., 2020; Gomez-Banuelos et al., 2024; Tanaka et al., 2023).

2.3 disease activity assessment

Disease activity was assessed using total SLEDAI score and retained urinary activity indicators. The SLEDAI and SLEDAI-2K remain widely used tools for quantifying SLE activity and for separating clinical activity from irreversible damage or inactive disease (Bombardier et al., 1992; Gladman et al., 2002; Suszek et al., 2024). Renal SLEDAI-related assessment commonly includes proteinuria, hematuria, pyuria and urinary casts, and each renal item is used to reflect active kidney involvement in SLE activity scoring (Mina et al., 2016; Yang et al., 2019; Amer et al., 2024). In this revised manuscript, C3, C4 and anti-dsDNA were intentionally removed from the analytical model according to the revised study plan, so the retained activity analysis focused on the clinical urinary indicators and total SLEDAI only.

III. RESULTS

3.1 Group comparison of serum IFN-alpha and IL-22

The SLE group showed a marked increase in serum IFN-alpha compared with controls. The mean IFN-alpha concentration was 57.42 ± 12.50 pg/mL in SLE patients and 7.38 ± 1.34 pg/mL in controls. The mean difference was 50.05 pg/mL (95% CI 46.03-54.07), with a very large effect size (Cohen d = 5.63). This direction agrees with the widely reported elevation of type I interferon activity and IFN-alpha-associated signatures in SLE compared with healthy or disease controls (Baechler et al., 2003; Kirou et al., 2005; Postal et al., 2020).

Interleukin -22 was also higher in the SLE group than controls (3.64 ± 1.34 vs. 2.54 ± 0.55 pg/mL), with a noted statistically significant p-value of 0.004. This result is consistent with reserches that report IL-22 or IL-22-producing CD4+ T-cell involvement in active SLE and lupus nephritis, although published IL-22 results remain heterogeneous through populations and clinical phenotypes (Zhao et al., 2013; El-Gazzar et al., 2017; Yang et al., 2019).

TABLE 1. Serum Cytokines in SLE Patients and Controls.

Marker	Group	n	Mean (pg/mL)	SD (pg/mL)	Mean ± SD (pg/mL)	p-value
IFN-alpha	SLE patients	40	57.42	12.50	57.42 ± 12.50	<0.001
IFN-alpha	Controls	40	7.38	1.34	7.38 ± 1.34	
IL-22	SLE patients	40	3.64	1.34	3.64 ± 1.34	0.004
IL-22	Controls	40	2.54	0.55	2.54 ± 0.55	

TABLE 2. SPSS-style independent-samples statistics.

Marker	Mean difference	t	df	95% CI lower	95% CI upper	Effect size	Sig.
IFN-alpha	50.05	25.17	39.89	46.03	54.07	Cohen d = 5.63	<0.001
IL-22	1.10	4.80	51.78	0.64	1.56	Cohen d = 1.07	0.004 reported

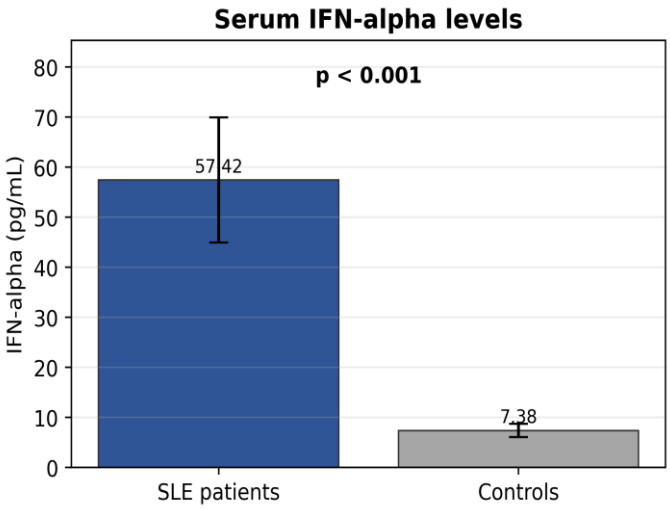

Figure 1. Mean serum IFN-alpha level in SLE patients and controls.

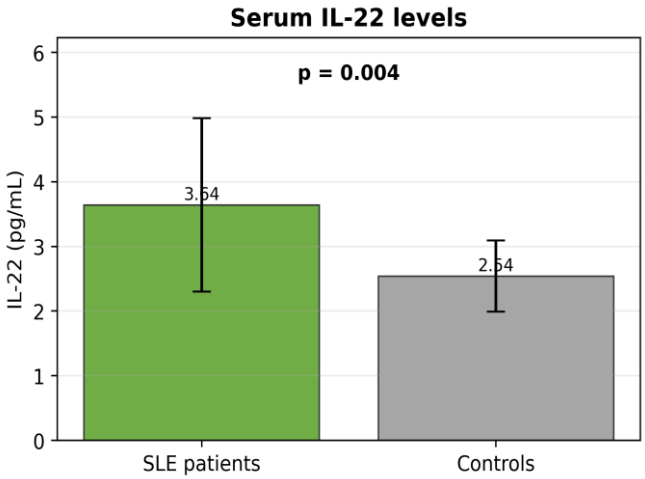

Figure 2. Mean serum IL-22 level in SLE patients and controls.

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3.2 Disease Activity Profile

The SLEDAI score in the SLE group was from 6 to 20, with a mean of 15.40 ± 2.45 and a median of 16.0. The distribution showed 1 moderate case (2.5%), 36 high-activity cases (90.0%), and 3 very-high-activity cases (7.5%). This predominantly active clinical profile is important because SLEDAI-based indices are intended to capture current inflammatory disease activity rather than chronic damage (Bombardier et al., 1992; Gladman et al., 2002; Suszek et al., 2024)

TABLE 3. Disease activity severity distribution among SLE patients.

Severity category	Number	Percentage
Moderate	1	2.5%
High	36	90.0%
Very High	3	7.5%
High + Very High	39	97.5%

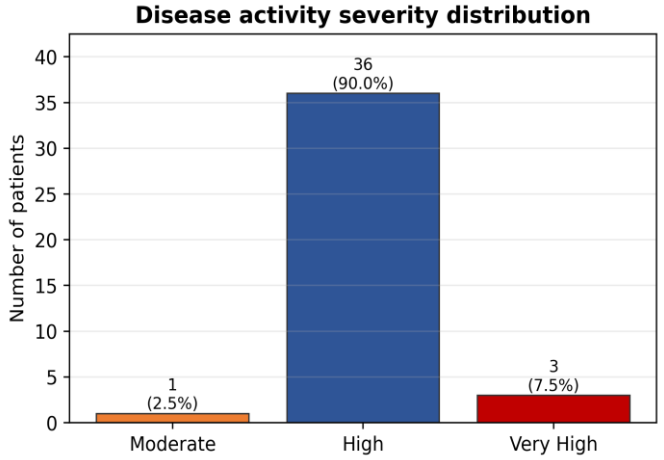

Figure 3. Professional bar chart showing disease activity categories.

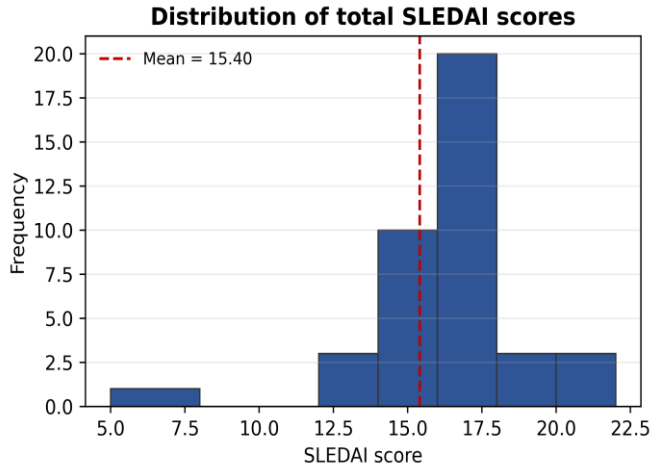

Figure 4. Distribution of total SLEDAI scores in SLE patients.

3.3 Relationship of retained variables with disease activity

Spearman correlation analysis showed that urinary activity indicators were more closely associated with total SLEDAI than IFN-alpha. Proteinuria score showed a significant positive correlation with total SLEDAI, and hematuria score showed a significant positive correlation with total SLEDAI. Urinary casts could not be tested because all patients had the same casts score in the provided dataset. IFN-alpha showed a weak, non-significant inverse correlation with total SLEDAI, indicating that although IFN-alpha was clearly elevated in SLE patients compared with controls, it did not vary linearly with SLEDAI within this patient group. Such a pattern is biologically plausible because type I interferon may identify a pathogenic subset or baseline inflammatory phenotype rather than precisely tracking short-term activity changes in every patient (Landolt-Marticorena et al., 2009; Postal et al., 2020; Gomez-Banuelos et al., 2024).

TABLE 4. Spearman correlation of retained variables with total SLEDAI score.

Variable	Spearman rho	p-value	Interpretation
Proteinuria score	0.539	<0.001	Significant positive
Hematuria score	0.484	0.002	Significant positive
Urinary casts score	Not applicable	Not applicable	Constant variable
IFN-alpha	-0.212	0.189	Not significant

TABLE 5. Spearman correlation with ordered activity severity category.

Variable	Spearman rho	p-value	Interpretation
Proteinuria score	0.736	<0.001	Significant positive
Hematuria score	0.862	<0.001	Significant positive
Urinary casts score	Not applicable	Not applicable	Constant variable
IFN-alpha	0.188	0.245	Not significant

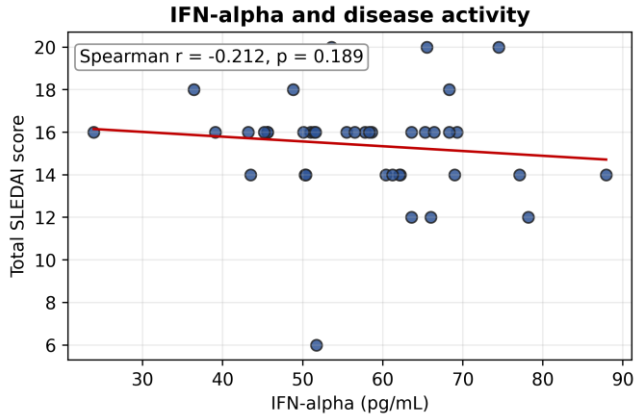

Figure 5. Scatter plot of IFN-alpha versus total SLEDAI score.

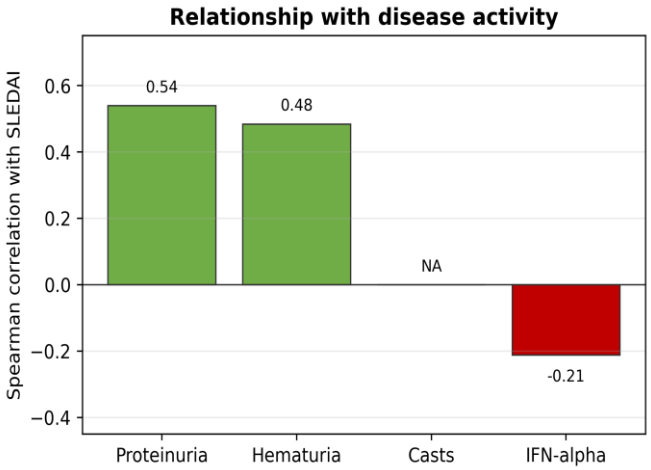

Figure 6. Correlation profile of retained variables with total SLEDAI score.

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3.4 IFN-alpha across activity severity categories

TABLE 6. IFN-alpha according to disease activity category.

Activity category	n	IFN-alpha Mean ± SD (pg/mL)
Moderate	1	51.70 ± NA
High	36	56.99 ± 12.75
Very High	3	64.53 ± 10.48

Kruskal-Wallis testing did not show a statistically significant difference in IFN-alpha across activity categories ($H = 1.45$, $p = 0.485$). This result should be interpreted cautiously because the moderate and very-high activity categories had small numbers of patients. Imbalanced activity categories reduce the power of non-parametric group comparisons and may obscure true biological gradients, particularly for cytokines that are heterogeneous across SLE subgroups (Landolt-Marticorena et al., 2009; Oke et al., 2019; Gomez-Banuelos et al., 2024).

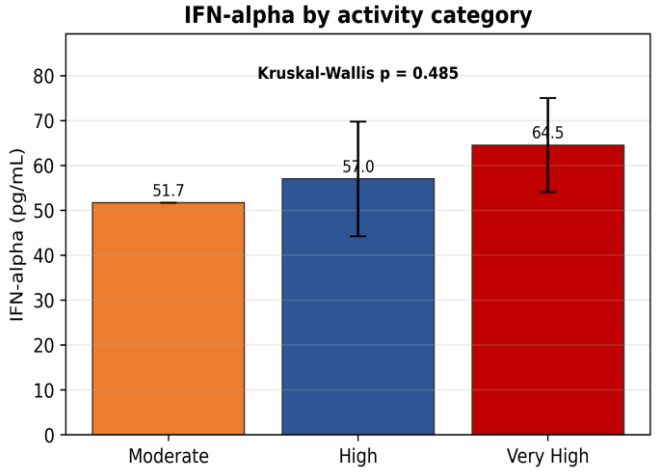

Figure 7. IFN-alpha distribution by disease activity category.

IV. Discussion

The revised analysis demonstrates that SLE patients had markedly higher serum IFN-alpha levels than controls. This finding is consistent with the established role of type I interferon activation in SLE, in which IFN-alpha promotes dendritic-cell activation, antigen presentation, B-cell survival, autoantibody-related immune amplification and IFN-stimulated gene expression (Baechler et al., 2003; Bennett et al., 2003; Postal et al., 2020). The magnitude of difference and very large effect size indicate that IFN-alpha clearly separated the SLE group from the healthy control group in this dataset, which agrees with previous studies reporting higher IFN-alpha pathway activity in active SLE than in control groups (Bengtsson et al., 2000; Kirou et al., 2005; Miyachi et al., 2023).

The IL-22 result also supported an inflammatory cytokine pattern in SLE, as the patient group showed higher IL-22 than the control group. IL-22 may reflect immune activation at epithelial and tissue interfaces, and its behavior in SLE may vary according to disease stage, organ involvement, treatment exposure and cytokine network balance (Zhao et al., 2013; Lin et al., 2014; El-Gazzar et al., 2017).

Therefore, the current result supports IL-22 as a potentially pertinent inflammatory marker (Lin et al., 2014; Yang et al., 2019).

The disease activity profile was predominantly active, with most patients classified as high or very-high activity. This pattern makes the elevated IFN-alpha and IL-22 biologically plausible because active SLE is commonly characterized by stronger innate immune activation, interferon signaling, and inflammatory cytokine networks (Kirou et al., 2005; Oke et al., 2019; Tanaka et al., 2023).

Proteinuria and hematuria showed significant positive relationships with total SLEDAI and ordered activity severity. This is expected because urinary abnormalities are important clinical manifestations of active lupus, particularly when renal involvement is present (Mina et al., 2016; Yang et al., 2019; Amer et al., 2024). In this dataset, the urinary indicators were more directly aligned with total disease activity than IFN-alpha itself, which is consistent with the scoring structure of renal SLEDAI components and with the clinical importance of urinary findings in lupus nephritis assessment (Bombardier et al., 1992; Gladman et al., 2002; Amer et al., 2024).

IFN-alpha was significantly elevated in SLE patients compared with controls, but its patient-level correlation with SLEDAI was not statistically significant. This does not contradict its pathogenic role; rather, it suggests that IFN-alpha may distinguish SLE from healthy status more strongly than it tracks small differences in SLEDAI within a group where most patients already have active disease (Landolt-Marticorena et al., 2009; Postal et al., 2020). The narrow severity distribution, duplicated activity patterns and treatment status may weaken within-group correlation, and recent evidence suggests that direct interferon measures and interferon signatures may define partially different SLE subgroups (Gomez-Banuelos et al., 2024).

Urinary casts could not be statistically correlated with activity because the casts score was constant across the patient dataset. In SPSS, a constant variable is excluded from correlation testing because it has no variance. Similarly, IL-22 could not be correlated directly with SLEDAI because individual IL-22 values were not supplied. For a stronger Scopus-level submission, the final dataset should include individual IL-22 values and demographic/clinical covariates such as age, sex, disease duration, treatment, renal involvement and medication exposure, as these covariates commonly influence cytokine-disease activity relationships in SLE studies (Oke et al., 2019; Miyachi et al., 2023; Suszek et al., 2024).

V. Conclusion

The revised manuscript shows that IFN-alpha and IL-22 are elevated in SLE compared with controls. Overall activity was high in most SLE patients. After restricting the model to retained activity variables, proteinuria and hematuria remained significantly associated with total SLEDAI and activity severity, while IFN-alpha did not show a significant within-patient correlation with SLEDAI. These results support a publishable cytokine-activity manuscript after completing missing clinical metadata and adding patient-level IL-22

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readings, especially because the current literature supports both IFN-alpha and IL-22 as biologically relevant but clinically heterogeneous immune markers in SLE (Postal et al., 2020; Yang et al., 2019; Gomez-Banuelos et al., 2024).

Limitations and recommendations before submission

The main limitation is that IL-22 was available only as group-level mean ± SD, which prevents valid correlation with SLEDAI. The activity categories were also imbalanced, with only one moderate case and three very-high cases. A final submission to a Scopus-indexed journal should include full demographic data, ethical approval details, diagnostic criteria, treatment status, ELISA kit details and a complete patient-level cytokine dataset. These recommendations are consistent with modern SLE biomarker studies, which usually combine cytokine measurements with validated classification criteria, disease activity scores, organ-involvement data and treatment information (Aringer et al., 2019; Oke et al., 2019; Miyachi et al., 2023).

Declarations

Ethics approval: this study was approved by Ethics committee of Jaber Ibn Hayyan for Medical and Pharmaceutical sciences.

Informed consent: written informed consent was obtained from all participants before sample collection.

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

Funding: this research received no external founding.

Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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