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Serum interferon-alpha predicts in-hospital mortality in patients hospitalised with acute severe lupus

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ABSTRACT

Objectives Dysregulation of interferon-alpha (IFN-α) is considered central to the immunological abnormalities observed in SLE. Short-term mortality during high disease activity in lupus is up to 30%. Adenovirus vector-introduced IFN-α into a lupus-prone mouse causes the development of glomerulonephritis and death within weeks. We studied serum IFN-α as a biomarker of in-hospital mortality in patients of SLE with high disease activity.

Methods Serum IFN-α (ELISA) was measured in patients hospitalised for acute severe lupus in a tertiary care rheumatology unit in India and the levels were compared between survivors and non-survivors. Serum IFN-α was compared with traditional clinical and serological markers associated with disease activity to assess which better prognosticates survival.

Results In a cohort of 90 patients with a mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of 19.3 (±5.5), the mean serum IFN-α was 88±144 pg/dL. Levels were undetectable in patients with inactive disease. SLEDAI, anti double stranded DNA (dsDNA) antibody titres and serum IFN-α levels were higher and serum complement (C3) lower in non-survivors (p=0.003, p=0.017, p<0.001, p=0.029, respectively). Serum IFN-α level of 140 pg/mL had a sensitivity of 86.7%, specificity of 94.6%, positive predictive value of 76% and negative predictive value of 83.3% (p<0.001) in predicting mortality. The area under the curve for predicting in-hospital mortality was 0.25 for C3, 0.72 for dsDNA, 0.77 for SLEDAI and 0.92 for serum IFN-α.

Conclusions Serum IFN-α was better in predicting in-hospital mortality compared with conventional measures of disease activity such as anti-dsDNA, complements and SLEDAI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interferon-alpha is believed to be central to lupus pathogenesis and high levels associate with active disease.
⇒ In animal models, interferon-alpha leads to severe glomerulonephritis and early death.
⇒ Serum interferon levels have not been specifically studied in hospitalised patients with lupus and neither were they correlated with outcomes.

WHAT THIS STUDY ADDS

⇒ We now know as a result of this study that serum interferon-alpha levels correlate better with in-hospital mortality than the Systemic Lupus Erythematosus Disease Activity Index, anti double stranded DNA (dsDNA) and complements.
⇒ Levels above 140 pg/mL predicted in-hospital mortality with high specificity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Serum interferon measured by ELISA at point of care might help triage patients to more aggressive therapy to control the disease.

INTRODUCTION

SLE is a prototype autoimmune disease characterised by a break of tolerance to nuclear components and profound alterations of the immune system. It is characterised by the presence of antinuclear autoantibodies and inflammation in a wide spectrum of organs. Dysregulation of interferons (IFNs), especially interferon-alpha (IFN-α), is considered a central cause of the immunological abnormalities observed in SLE. Raised levels of serum IFN-α have been observed in patients with active SLE.[1] Transcriptome analysis using microarray technology revealed upregulation of the expression of numerous IFN-stimulated genes in the peripheral blood mononuclear cells of patients with SLE, constituting an overall 'IFN signature'.[2 3] This signature is found in almost all paediatric patients and 50%–80% of adults with SLE.[4] IFN-α, as a central mediator in the pathogenesis of SLE, is identified through advances in the understanding of innate immunity by Toll Like Receptor (TLR) 7,9 pathways and along with insights gained from analysis of gene transcripts induced by IFN-α.[5] IFN-α can induce autoantibodies and clinical lupus in humans.[6] Anifrolumab is a monoclonal antibody that targets the type I IFN receptor and has shown effectiveness in reducing disease

activity in patients with SLE and has been approved by the Food and Drug Administration (FDA) for treatment of SLE. It was observed in mouse studies that when IFN-α was delivered through an adenovirus vector to a lupus-prone mouse, it caused rapid development of glomerulonephritis and death within 18 weeks. Short-term mortality of patients of SLE with high disease activity reported in very few studies may be as high as 30%.[7 8] We studied the utility of serum IFN-α in patients of SLE with high disease activity as a biomarker predictive of in-hospital mortality.

MATERIALS AND METHODS

Patients in a tertiary care rheumatology unit in India between 18 and 65 years of age who satisfied the Systemic Lupus International Collaborating Clinics[9] or the 1997 update of the 1982 American College of Rheumatology[10] classification criteria for SLE and with high disease activity (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2K >12)[11] were enrolled in the study between November 2020 and December 2021. Patients or their legal representatives were informed of the research and each provided written information in their native languages. Patients were not involved in the study design. If accepted by peer review, the public will be informed of the results through social media.

Patients in remission or with mild/moderate flare according to the SELENA-SLEDAI index (<12), those with overlap syndromes or hospitalised for an infection, malignancy or for any cause unrelated to disease activity, or were unwilling to provide informed consent were excluded from this study. On clinical suspicion of infection, appropriate tests, including at the minimum blood culture, urine culture and procalcitonin, were used. When needed, bronchial aspirate culture, tissue culture and any other relevant tests, including serology for establishing routine and opportunistic infections, were used. Demographic data, clinical details and laboratory investigations were noted. Serum complements were measured through nephelometry (Beckman Coulter; normal range: 90–180 mg/dL for C3 and 10–40 mg/dL for C4), as well as anti double stranded DNA (dsDNA) antibodies through ELISA (Calbiotech; normal range <0.9 OD). Simultaneously, serum was stored at −80 to measure IFN-α level. Disease activity for each patient was recorded using SLEDAI 2K and the British Isles Lupus Assessment Group (BILAG) 2004 instrument.[12] In the BILAG instrument, 97 glossary-defined items of disease activity are grouped under nine domains. These domains were used to report the clinical characteristics of the patients. Death during hospitalisation for current illness was classified as short-term mortality. Patients who were discharged were considered survivors, while those who succumbed during admission were considered non-survivors. Serum IFN-α levels were also measured in 10 patients with low disease activity (SLEDAI <4).

Serum IFN-α detection method

Blood samples were collected from each patient into a red tube and centrifuged at 2500 rpm for 15 min. Serum was collected and assayed using the ELISA method (Elabscience IFN-α kits with a detection range of 7–500 pg/mL), following the manufacturer's instructions. The samples were diluted and added to appropriate wells in a plate which was then sealed and incubated for 90 min at 37°C. The wells were washed and treated with detection and conjugate working solutions before adding substrate reagent and incubating for 15 min. The optical density (OD) of each well was measured at 450 nm using a microplate reader. The IFN-α levels were calculated by plotting a four-parameter logistic curve on log-log graph paper using the average OD values of the standards. The technician doing the assay was blind to the outcome of the patient.

Statistical analysis

Normality was assessed by the Shapiro-Wilk test. Continuous normally distributed variables were expressed as mean and SD. Comparison between two groups of normally distributed data was addressed by t-test. For comparison of two groups of non-normally distributed ordinal variables, the Mann-Whitney test was used. A p value <0.05 was considered a significant difference. Receiver operating characteristic curves (ROC) were plotted to explore the significance of various variables in predicting death. The sensitivity and specificity of the IFN-α level to predict death were determined by the ROC curve. Simple regression was used to find associations of IFN-α with different disease domains. Binomial logistic regression was used to predict in-hospital mortality with different variables.

RESULTS

One hundred and eighteen patients with SLE with high disease activity were initially screened for eligibility. Patients under 18 years, those with overlap syndrome and those with infections were excluded, resulting in a final study cohort of 90 patients. Among these patients, 75 were female and 15 were male, with a female to male ratio of 5:1. The patients had a mean (±SD) age of 27.6 (±8) years. The mean duration of disease and of hospital stay was 27 (±27) months and 8.8 (±4.4) days, and the mean SLEDAI was 19.3 (±5.5). The mean (SD) levels of dsDNA, C3 and C4 were 2 (±1.8), 44.3 (±11.1) mg/dL and 11.9 (±9.5) mg/mL, and the serum IFN-α level was 88±144 pg/mL.

Of the enrolled patients, 82 were admitted to the ward, while 8 were directly admitted to the intensive care unit (ICU). Renal involvement was the most common manifestation, observed in 76% of patients, followed by musculoskeletal, haematological, mucocutaneous, cardiovascular, gastrointestinal and neuropsychiatric involvement in 62%, 58%, 54%, 28%, 15% and 13% of patients, respectively (refer to table 1).

Table 1 Baseline characteristics of all subjects

Demographic details	Mean (SD)
Age (years)	27.6 (±8)
Duration of disease (months)	27 (±27)
Hospital stay (days)	8.8 (±4.4)
Mucocutaneous involvement (%)	54
Musculoskeletal involvement (%)	62
Neuropsychiatric involvement (%)	13
Gastrointestinal involvement (%)	15
Cardiovascular involvement (%)	28
Renal involvement (%)	76
Haematological involvement (%)	58
Anti-dsDNA (normal <0.9)	2 (±1.8)
C3 (mg/dL)	44.3 (±11.1)
C4 (mg/dL)	11.9 (±9.5)
Serum IFN-α (pg/mL) Median (range)	88 (±144) 14 (7–95)

dsDNA, double stranded DNA.

Out of the 90 patients, 75 (83%) were discharged from the hospital and hence called survivors, while 15 died in the hospital. The major causes of death were diffuse alveolar haemorrhage in three patients, severe pulmonary arterial hypertension in two, pancreatitis in three, acute kidney injury in seven, thrombotic thrombocytopaenic purpura in one and myocarditis in six.

Parameters were compared between survivors and non-survivors (table 2). There was no significant difference in age between the two groups. The hospital stay was significantly shorter for non-survivors. There was no significant difference in disease duration between the two groups. The non-survivor group had a higher percentage of mucocutaneous (73% vs 50%) and musculoskeletal (80% vs 58%) involvement compared with the survivors, although the differences were not statistically significant. The SLEDAI and antibodies to dsDNA were significantly higher and C3 levels lower in non-survivors. Serum IFN levels were significantly higher in the non-survivor group (335±176 pg/mL) compared with the survivor group (38.9±67.6 pg/mL) (p<0.001).

IFN-α levels

The kit used to measure IFN-α levels had a range of 7–500 pg/mL. Among 90 patients, the mean (±SD) serum IFN-α level was 88.8 (±144) pg/mL. Thirty-nine had undetectable (<7 pg/mL) serum IFN-α levels (38

Table 2 Comparison of parameters between survivors and non-survivors

Variables	Survivors (n=75) Mean (±SD)	Non-survivors (n=15) Mean (±SD)	P value
Age (years)	27.87 (±7.89)	28.1 (±11)	0.947
Hospital stay (days)	9.25 (±4.9)	4.4 (±1.96)	**<0.001**
Disease duration (months)	29.2 (±28.4)	17.1 (±16.1)	0.11
dsDNA	1.77 (±1.82)	3.15 (±1.88)	**0.017**
SLEDAI	18.44 (±5.25)	23.6 (±5.44)	**0.003**
Number of organs involved	4.6 (±1.2)	5.8 (±1.1)	0.102
Mucocutaneous involvement (%)	50	73	0.101
Musculoskeletal involvement (%)	58	80	0.109
Neuropsychiatric involvement (%)	12	20	0.39
Gastrointestinal involvement (%)	14	20	0.40
Cardiovascular involvement (%)	26	40	0.55
Renal involvement (%)	76	86	0.27
Haematological involvement (%)	56	80	0.08
Interferon (pg/mL)	38.9 (±67.6)	335 (±176)	**<0.001**
Complement C3 (mg/dL)	47.2 (±25.3)	30.1 (±25.7)	**0.029**
Complement C4 (mg/dL)	11.6 (±9.3)	8.9 (±10.5)	0.356
TLC	5707 (±3872)	5108 (±3560)	0.564
Creatinine (mg/dL)	0.946 (±0.603)	1.52 (±1.09)	0.067
Serum albumin (g/dL)	2.744 (±0.695)	2.4 (±0.607)	0.064
SPCR	1.61 (±1.85)	1.7 (±1.96)	0.889

P values in bold (<0.05).
dsDNA, double stranded DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SPCR, spot protein creatnine ratio; TLC, Total Leucocyte Count.

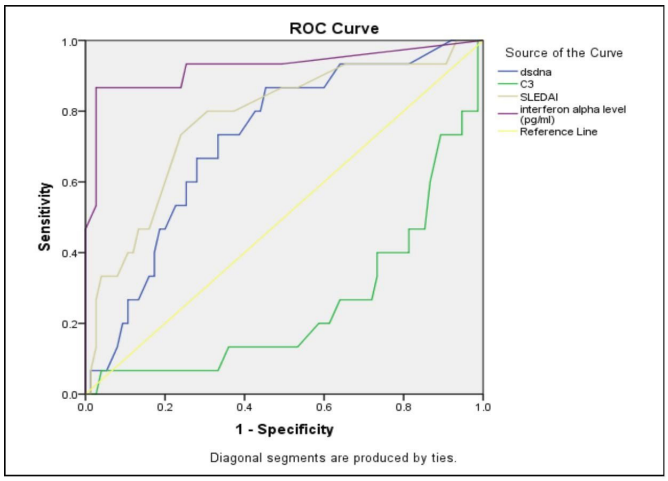

Figure 1 ROC curves for C3, dsDNA, SLEDAI and IFN-α. The area under the curve for C3 is 0.25, anti-dsDNA 0.72, SLEDAI 0.77 and IFN-α 0.92. IFN-α, interferon-alpha; ROC, receiver operating characteristic; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

survivors and 1 non-survivor). Six patients with serum IFN-α levels beyond 500 pg/mL were all non-survivors. In two of the patients with levels greater than 500 pg/mL, the final serum IFN-α was 16 700 pg/mL (1:50 dilution) and 3875 pg/mL (1:25 dilution). These two patients had anti-dsDNA levels of 4.7 and 5, SLEDAI scores of 28 and 30, C3 levels of 36 mg/dL and 15 mg/dL, and C4 levels of 4 mg/dL and 5 mg/dL, with cardiovascular, neurological and renal manifestations. Patients with IFN-α levels above 500 pg/mL had higher mean dsDNA (3.5) and SLEDAI (25.8) compared with those with undetectable IFN-α levels (mean dsDNA of 0.9 and SLEDAI of 16.9). In addition, all 10 patients with low disease activity (SLEDAI <4) had undetectable serum IFN-α levels.

Correlation between IFN-α level and BILAG disease activity

A simple regression analysis was conducted to examine the relationship between IFN-α levels and scores in various BILAG domains, including constitutional, mucocutaneous, musculoskeletal, gastrointestinal, neuropsychiatric, cardiovascular, ophthalmology, renal and haematological domains. The results showed that high levels of IFN-α were significantly associated with increased scores in the renal, haematological and neuropsychiatric domains (p=0.008, p=0.017 and p=0.001, respectively).

Serum IFN-α as a predictor of mortality

The following variables were analysed as predictors of mortality: IFN-α, SLEDAI, C3, C4, dsDNA, duration of hospital stay and age, and their p values from the univariate analysis were <0.001, 0.01, 0.02, 0.36 and 0.01, respectively. In the binomial logistic regression, IFN-α, dsDNA, C3 and SLEDAI predicted in-hospital mortality. The p value for serum IFN-α was <0.001, while the p values for dsDNA, SLEDAI and C3 were 0.4, 0.5 and 0.09, respectively. The ROC curves were plotted for dsDNA, SLEDAI, IFN-α and C3 for predicting mortality. The area under the curve (AUC) was 0.25 for C3, 0.72 for dsDNA, 0.77 for SLEDAI and 0.92 for serum IFN-α, indicating that it was the best predictor of mortality. Serum IFN-α level of 140 pg/mL has a sensitivity of 86.7%, specificity of 94.6%, positive predictive value of 76% and negative predictive value of 83.3% (p<0.001) in predicting mortality (figure 1).

DISCUSSION

This study was intended to record serum IFN-α levels in patients with SLE admitted to hospital with high disease activity (SLEDAI >12). We observed the mean serum IFN value was significantly higher in non-survivors than in survivors. Serum IFN-α was also a better predictor of in-hospital mortality than global disease activity markers like SLEDAI or serological markers like dsDNA and C3.

Studies on in-hospital mortality in patients with acute severe lupus have been the scope of a systematic review. The median mortality rate of patients with SLE admitted to ICU was around 30% (IQR 24%–47%).[13] No unique biomarkers were reported in any of these studies. In global studies investigating the impact of high disease activity on mortality of patients with lupus, variations in outcomes have emerged. The fraction of mortalities attributable to high disease activity ranges from 12% in China[14] to 55% in a comprehensive multicentric study in India,[15] with other studies in the USA,[16] Spain[17] and Canada[18] reporting rates of 4%, 6.4% and 13.3%, respectively. In a tertiary setting in India,[19] 61% of patients with high disease activity succumbed during their first hospital visit, even as admission patterns frequently involved a transition from general wards to ICU based on health deterioration.

Working on the hypothesis that in vivo impregnation of IFN-α in lupus-prone mice might represent a model of IFN-α dysregulation seen in human lupus, Mathian *et al*[20] showed that administration of IFN-α induces early lupus in preautoimmune mice, with death within 18 weeks.

There is no literature studying serum IFN-α level in severe active lupus and correlating it with survival. We demonstrate that serum IFN-α was much higher in those who died during an episode of acute severe lupus.

In another study conducted by Mathian *et al*,[21] digital ELISA was used for serum IFN-α detection and the abnormality threshold was 0.136 pg/mL and the median value in patients with active lupus was 1.36 pg/mL. We used an ELISA, which is not the most sensitive assay, yet we found levels which were much higher than reported by Mathian *et al*.[21] Higher levels of serum IFN-α have been previously reported in patients with high disease activity.[22]

Circulating IFN-α levels have been correlated with disease activity in various domains. Oke *et al*[23] reported high serum IFN-α was associated with mucocutaneous disease, lymphadenopathy and anti-La antibodies. Bengtsson *et al*[24] reported that patients with a history of haematological manifestation had significantly higher levels of IFN-α activity (p=0.002). Mathian *et al*[21] showed

that abnormal serum IFN-α levels (as measured by digital ELISA) were associated with fever, mucocutaneous manifestations and active lupus nephritis. Dall'era *et al*[22] also showed a similar association between IFN-α levels (as measured by a reporter assay) and mucocutaneous manifestations, SLEDAI and anti-dsDNA levels. We also found a positive correlation between serum IFN-α, dsDNA and SLEDAI. In our study, IFN-α levels correlated with renal, haematological and neurological manifestations. Ytterberg and Schnitzer[1] found measurable amounts of IFN-α (as measured by antiviral assays) in 76.6% of active lupus compared with 9.1% during disease quiescence. In a group of 10 patients in our study chosen for having low disease activity, none showed measurable serum IFN-α levels.

In some studies, longitudinal assays of IFN-α have been reported. In a study of 30 patients with SLE where serial serum IFN-α levels were measured, Bengtsson *et al*[24] determined that flare levels of IFN-α were higher and correlated with SLEDAI, dsDNA and hypocomplementaemia (C3) and with more rash, but not with nephritis.

Mathian *et al*[21] compared the ROC AUC for the IFN-α digital ELISA, IFN bioassay and Farr assay (dsDNA) and showed that both digital ELISA and bioassay were better biomarkers than Farr assay in differentiating between active and inactive SLE and flare versus no flare. They concluded that IFN-α by ELISA or bioassay had a higher specificity and positive likelihood ratio compared with dsDNA in predicting disease activity. In our study, we found that serum IFN-α by ELISA had a higher AUC (0.92) compared with dsDNA (0.72), implying its role as a better predictor of disease activity and in-hospital mortality. When binomial logistic regression was applied to predict in-hospital mortality, serum IFN-α was significantly better at predicting in-hospital mortality compared with C3, dsDNA and SLEDAI.

Apart from ELISA, measurement of IFNs has been done using bead-based ELISA (SIMOA, single molecule array, with the ability to detect IFN-α in the femtomolar range) and the IFN-α bioassay (treatment of IFN-α-responsive cells with test samples and known lab standards to determine IFN-α activity). These have disadvantages of cross-reactivity with other cytokines, expensive training and varying biological activity. Interferon gene signature (IGS) can be measured using microarray analysis, quantitative (q)PCR and RNA sequencing, but they are also time-consuming, costly and are highly specialised.

Since patients with proven or suspected infection were excluded, these results can be generalised only to patients with lupus who are critically ill due to disease but not infection.

To our knowledge, this is the first study to demonstrate that patients hospitalised with severe acute lupus who died during hospitalisation had much higher serum IFN-α levels than those who survived.

CONCLUSION

The ELISA-detected levels of serum IFN-α were found to be markedly elevated in individuals with active lupus and were significantly higher than in those who survived the episode of severe lupus. This biomarker demonstrated a superior ability to predict in-hospital mortality compared with conventional measures of disease activity such as anti-dsDNA, complements and SLEDAI. These findings suggest that serum IFN-α may serve as a valuable prognostic biomarker in the early stages of severe active lupus, allowing for more aggressive disease management and treatment strategies. If reproduced, ELISA assays which are easy to do may provide a valuable alternative to IGS studies as real-time predictors of outcome during severe lupus flare. Overall, these findings highlight the potential clinical utility of serum IFN-α as a powerful tool for enhancing the accuracy of lupus prognosis and disease management.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Nizam's Institute of Medical Sciences Institutional Ethics Committee (approval number 2614/2020). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request.

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