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Serum Inflammatory Cytokines as Dual Biomarkers in Systemic Lupus Erythematosus and Breast Cancer Progression

Abdulrhman M. Hassan[1]

[1] College of Medicine, Al-Nahrain University

Email corresponding author: abdulrhman.m.hadi@nahrainuniv.edu.iq

Abstract. General Background: Chronic inflammation plays a critical role in both autoimmune diseases and cancer, where cytokines act as key mediators of immune dysregulation. Specific Background: Systemic Lupus Erythematosus (SLE) and breast cancer, despite differing etiologies, share overlapping mechanisms of cytokine imbalance that drive disease progression and immune modulation. Knowledge Gap: However, the potential of inflammatory cytokines as dual biomarkers reflecting both autoimmune and tumor-related processes remains underexplored. Aims: This study aimed to evaluate serum levels of IL-6, TNF-α, IL-1β, IL-8, IL-10, and TGF-β in SLE and breast cancer patients compared to healthy controls, and to analyze their correlation with disease duration. Results: Findings demonstrated significantly elevated pro- and anti-inflammatory cytokine levels in both patient groups ($p < 0.001$), with strong positive correlations between cytokine concentration and disease duration. Breast cancer patients showed higher IL-6, TNF-α, and TGF-β levels, while SLE patients exhibited pronounced immune activation. Novelty: The study provides the first integrated evaluation of cytokine profiles revealing shared inflammatory signatures in autoimmunity and oncogenesis. Implications: These results highlight cytokines' potential as diagnostic and prognostic biomarkers, suggesting that cytokine modulation may offer novel therapeutic targets for both SLE and breast cancer.

Highlights:

1. Cytokines act as dual biomarkers indicating immune activation in both SLE and breast cancer.
2. Pro- and anti-inflammatory cytokines correlate positively with disease duration and progression.
3. The study highlights cytokines' potential roles in diagnosis, prognosis, and therapeutic targeting.

Keywords: Systemic Lupus Erythematosus, Breast Cancer, Inflammatory Cytokines, IL-6, TNF-α

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Introduction

In the acute phase, cytokines and chemokines induce an inflammatory response that is characterized by local as well as systemic responses. Systemic lupus erythematosus (SLE) is the paradigm of multi-organ autoimmune disease, with autoantibody production, immunocomplex deposition and inflammatory cell attractment. In the same course, breast cancer is the most common cancer in women and being caused by multiple factor interaction of the genetics, hormones and local inflammatory microenvironment 1. Though, pathophysiology of the diseases are different, they all tends to the same direction i.e., towards immune dysregulation and overproduction of pro-inflammatory cytokines. This intersection suggests that inflammatory cytokines may serve as dual biomarkers echoing the activity of autoimmune processes and determining the direction of neoplastic progression [3].

These are the small signal proteins that are made and secreted by immune- and non-immune-cells-called cytokines, playing an essential role in the communication between cells and activation of the defense. These are pleiotropic, context-dependent pro- and anti-inflammatory effects. The systemic lupus erythematosus (SLE) with its inherent imbalance between these networks of synergies and antagonisms among cytokines promotes an exaggerated immune hyperactivation and leads to the production of autoantibodies and tissue damage [4]. Similarly, inflammatory cytokines are dominant elements of the transcriptional niche in breast cancer microenvironments supporting tumor growth and angiogenesis promotion, invasion and immune evasion. Thus, an analysis of the cytokine profiles in these two completely different forms of diseases may provide a useful indicator of pathophysiologies associated with such diseases, and open up new possibilities for their treatment and diagnosis 5.

Several cytokines were determined to be integrators of core significance in the context of complexity between SLE and breast cancer. Il-6: a pleiotropic cytokine that activates B-cell, promotes their differentiation and survival in the course of SLE, but also enhances growth and metastasis of breast tumors by mediating activation of STAT3 signaling 7. Relationship of TNF and TNF- alpha in the SLE and breast cancer: Tumor necrosis factor alpha (TNF- alpha) a pro-inflammatory cytokine functions as tissue destroying inflammatory both locally and systemically in patients with SLE while it has the role of tumorigenesis, cell proliferation, angiogenesis promoting agent among reasive oxygen species production by-products for breast cancer. Moreover, interleukin-1 beta (IL-1) and interleukin-8 (IL-8) are key players that trigger a positive feed-back loop of proliferative bursts and promotion of cancerous cells' migration and metastasis, respectively [9]. On the other hand, regulatory molecules, including Interleukin-10 (IL-10) and Transforming growth factor beta (TGF-alpha) have an anti-inflammatory effect. The immunosuppressive effect of IL-10 in systemic lupus erythematosus (SLE) is based on the fact that the cytokine reduces the risk of tissue destruction by hyper-inflammatory processes, although in breast cancer, IL-10 facilitates tumor growth to circumvent immunosurveillance [10]. TGF-B may also work in both directions, so that it reduces inflammation and autoimmunity, but enhances incidences that lead to the esophagus experiencing an esophquelial mesenchymal transition, tumor growth, and metastasis[11][12].

They may be surrogate markers of the activity of systemic diseases and can provide valuable prognostic information if they are not invasive. Supporting this, profiling of serum

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cytokines has correlated with flares and end-organ damage in systemic lupus erythematosus (SLE) and response to therapy. Similarly, the levels of cytokines are also considered as surrogate endpoints of disease burden, res ponse to treatment and aggressiveness in BC [13] [14].

Although spontaneous uncontrolled protests leading to violent responses are still studied by social scientists today,meantime, progress of scientific research has indeed remained remarkably quiet about the details of inflammatory cytokines being regarded mutually as biomarkers in autoimmunity and cancers 15]. A broader definition of the cytokine profile posed in SLE and breast cancer is presumably to assistance in revealing shared immunopathogenic paths as well as identifying possible candidates for therapy intervention. In addition, monitoring of these biomarkers might help in differentiating between disease fluctuations and very slowly progressing courses of the disease that could improve control on an individual patient basis and allow to tailor a more personalized treatment strategy [16].

This study seeks to evaluate the levels of serum IL-6, TNF-alpha, IL-1-beta, IL-8, IL-10 and TGF-beta in patients with systemic lupus erythematosus (SLE) versus breast cancer and compare them with healthy controls for their dual biomarker roles which can be both inflammatory and cancer-related.

Methodology

The study was an observational cohort study conducted between March 10, 2025 - September 20, 2025 at two centers (Al-Habboubi Teaching Hospital and Nasiriyah General Hospital). Consecutive 60 subjects, assigned to two cohorts namely Suspected SLE (n=30) and Suspected Breast Cancer (SBC), along with twenty five age and sex matched healthy controls were included. Participants ranged in age from 25 to 60. The inclusion criteria required a confirmed diagnosis by an experienced specialist, no acute infectious processes and no use of immunomodulating or anti-inflammatory substances within the previous weeks. On the other then, exclusive criteria were pregnancy, any additional autoimmune or malignant diseases and related associated permanent condition i.e., hepatic or renal insufficiency. All the subjects were maintained strictly using aseptic precautions and venous blood samples (5 mL) were collected in ordinary gel vials. The samples were kept at room temperature for incubation for coagulation followed by centrifugation to 3000 rpm and for 10 min in order to obtain the serum which was, then, deposited in microtubes and stored at-20 o C until processing. Serum level of inflammatory cytokine (IL-6, TNF-a, IL-1b, IL-8, IL-10 and TGF-B) levels were quantified by ELISA according to manufactures' protocol using ((R&D Systems Inc., Minneapolis MN www.rndsystems.com), with quality control being assured at each stage.

Statistical analysis:

Quantitative data was also analyzed in data analysis stage using SPSS model 26 which is an established statistical analysis software program. Results are presented in the form of frequencies and percentages. Independent and dependent t-test two tails were executed under the conditions of normal distribution of the variables. Where normality was not observed with the variables other methods (Mann-Whitney U, Wilcoxon and Chi-

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square test) were used in order to allow a comprehensive analysis. The results were also validated by using p-value < 0.05 as a cut-off of statistical significance.

Results

Baseline demographic variable comparison between patients with Systemic lupus erythematotus, Breast cancer, and healthy control group.

The outcome of demographic analysis indicated that there were considerable differences between the study groups in the age, body mass index (BMI), and gender. The mean age of systemic lupus patients was 38.6 ± 9.2 years, while it was higher in breast cancer patients (47.8 ± 10.1 years), compared to the control group (36.5 ± 8.4 years), with a statistically significant difference (p = 0.001).[17] The proportion of females was also high in all groups, reaching 100% in the breast cancer group, 83.3% in the lupus group, and 84.0% in the control group (p = 0.041). BMI showed a significant increase in breast cancer patients (28.6 ± 3.8) kg/m² compared to the lupus (25.4 ± 3.1) and control (24.9 ± 2.9) groups, with a statistical significance (p = 0.009). As for the percentage of smokers, no significant differences were recorded (p = 0.182). The average duration of the disease (in years) was 5.6 ± 2.4 in lupus patients and 4.8 ± 2.1 in breast cancer patients, without significant differences (p = 0.217).

Table 1: Sociodemographic Characteristics of the Study Population

Variable	SLE Patients (n = 30)	Breast Cancer Patients (n = 30)	Control (n = 25)	p-value
Age (years, Mean ± SD)	38.6 ± 9.2	47.8 ± 10.1	36.5 ± 8.4	0.001
Gender (Female % [n])	83.3% (25)	100% (30)	84.0% (21)	0.041
BMI (kg/m², Mean ± SD)	25.4 ± 3.1	28.6 ± 3.8	24.9 ± 2.9	0.009
Smoking Status (Yes % [n])	20.0% (6)	30.0% (9)	12.0% (3)	0.182
Disease Duration (years, Mean ± SD)	5.6 ± 2.4	4.8 ± 2.1	—	0.217

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Comparison of serum concentrations of pro-inflammatory cytokines between patients with Systemic lupus erythematosus, Breast cancer, and healthy controls

Serum inflammatory cytokines showed a significant increase in the levels of all inflammatory markers among the study groups. Breast cancer patients had the highest mean interleukin-6 concentration (41.2 ± 10.5) pg/ml, followed by lupus patients (34.8 ± 8.2), while the lowest level was in the control group (12.5 ± 4.3), with a highly significant difference ($p < 0.001$). As for tumor necrosis factor (TNF-α), the mean concentration was (52.3 ± 12.6) pg/ml in breast cancer patients and (48.5 ± 11.4) in lupus patients, compared to (18.9 ± 6.2) in the control group ($p < 0.001$). A significant increase in IL-1β and IL-8 levels was observed in both disease groups compared to the control group, with the average IL-1β levels being (29.1 ± 8.0) and (26.3 ± 7.5) pg/ml versus (10.2 ± 3.7) in the control group, while IL-8 levels were (50.6 ± 13.3) and (45.9 ± 12.8) versus (20.4 ± 7.1), respectively, with highly statistically significant differences ($p < 0.001$) for all indicators. These results indicate a higher inflammatory activity associated with both disease conditions compared to healthy individuals.Table(2)

Table 2: Serum Pro-inflammatory Cytokine Levels among Study Groups

Cytokine (pg/mL)	**SLE Patients (n = 30) Mean ± SD**	**Breast Cancer Patients (n = 30) Mean ± SD**	**Control (n = 25) Mean ± SD**	**p-value**
Interleukin-6 (IL-6)	34.8 ± 8.2	41.2 ± 10.5	12.5 ± 4.3	<0.001
Tumor necrosis factor alpha (TNF-α)	48.5 ± 11.4	52.3 ± 12.6	18.9 ± 6.2	<0.001
Interleukin-1 beta (IL-1β)	26.3 ± 7.5	29.1 ± 8.0	10.2 ± 3.7	<0.001
Interleukin-8 (IL-8)	45.9 ± 12.8	50.6 ± 13.3	20.4 ± 7.1	<0.001

Comparison of serum concentrations of anti-inflammatory cytokines between patients with Systemic lupus erythematosus, Breast cancer, and healthy controls

Serum anti-inflammatory cytokines measured significantly higher levels of both IL-10 and TGF-β in patients compared to the control group. The mean IL-10 concentration in breast cancer patients was 24.6 ± 7.4 pg/ml, and in systemic lupus patients was 22.1 ±

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6.8 pg/ml, while the lowest concentration was in the control group (11.3 ± 3.5 pg/ml), with highly statistically significant differences ($p < 0.001$). A similar increase in TGF-β levels was observed, reaching 42.9 ± 12.1 pg/ml in the breast cancer group and 38.7 ± 10.2 pg/ml in the lupus group, compared to 21.8 ± 6.9 pg/ml in the control group, with highly statistically significant differences ($p < 0.001$). These results indicate an anti-inflammatory immune response associated with both disease states.Table(3)

Table 3: Serum Anti-inflammatory Cytokine Levels among Study Groups

Cytokine (pg/mL)	**SLE Patients (n = 30) Mean ± SD**	**Breast Cancer Patients (n = 30) Mean ± SD**	**Control (n = 25) Mean ± SD**	**p-value**
Interleukin-10 (IL-10)	22.1 ± 6.8	24.6 ± 7.4	11.3 ± 3.5	<0.001
Transforming growth factor beta (TGF-β)	38.7 ± 10.2	42.9 ± 12.1	21.8 ± 6.9	<0.001

Correlation between Serum Cytokine Levels and Disease Duration

Correlation analysis results showed a statistically significant positive relationship between inflammatory and anti-inflammatory cytokine levels and disease duration in patients with systemic lupus erythematosus (SLE) and breast cancer. A strong correlation was observed between IL-6 and disease duration ($r = 0.58$, $p = 0.001$) in lupus and ($r = 0.49$, $p = 0.006$) in breast cancer. A stronger correlation was also observed with TNF-α ($r = 0.61$, $p < 0.001$) and ($r = 0.52$, $p = 0.004$), respectively. For IL-1β, the correlation coefficients were (0.55, $p = 0.002$) and (0.47, $p = 0.008$) in both groups. As for anti-inflammatory cytokines, IL-10 showed a moderately strong correlation with disease duration ($r = 0.43$, $p = 0.015$) in lupus and ($r = 0.39$, $p = 0.027$) in breast cancer, while TGF-β recorded a relatively weaker statistically significant correlation ($r = 0.40$, $p = 0.022$) and ($r = 0.36$, $p = 0.041$), respectively. These results reflect the role of cytokines in disease progression and severity over time.Table(4)

Table 4: Correlation analysis of serum cytokine concentrations with disease duration in patients with Systemic lupus erythematosus and Breast cancer

Cytokine (pg/mL)	**SLE Patients (n=30) r (p-value)**	**Breast Cancer Patients (n=30) r (p-value)**
IL-6	r = 0.58 (p = 0.001)	r = 0.49 (p = 0.006)
TNF-α	r = 0.61 (p < 0.001)	r = 0.52 (p = 0.004)
IL-1β	r = 0.55 (p = 0.002)	r = 0.47 (p = 0.008)

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IL-10	r = 0.43 (p = 0.015)	r = 0.39 (p = 0.027)
TGF-β	r = 0.40 (p = 0.022)	r = 0.36 (p = 0.041)

Discussion

In the current investigation, significantly heightened serum levels of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IL-8) are observed, alongside, intriguingly, elevated concentrations of anti-inflammatory factors (IL-10, TGF-β) in cohorts suffering from systemic lupus erythematosus (SLE) and breast cancer when juxtaposed with healthy individuals. This observation is congruent with a substantial body of literature that underscores systemic immune activation as a hallmark of SLE, while simultaneously revealing that a pro-tumorigenic inflammatory environment is a characteristic feature of breast cancer advancement. Notably, elevated IL-6 levels in SLE have been consistently documented and correlated with disease severity, B-cell hyperactivity, and organ involvement; in a parallel vein, circulating IL-6 has been linked to aggressive tumor behavior and adverse prognostic outcomes in breast cancer scenarios [18][19].

In our analyzed populations, we observed an elevation in TNF-α levels, which exhibited one of the most pronounced associations with the duration of the disease [20]. Previous investigations lend credence to the notion that TNF-α serves as a pivotal differentiator between individuals afflicted with systemic lupus erythematosus (SLE) and healthy controls, further implicating it in the pathophysiology of lupus-related tissue damage and its extrarenal manifestations. Within the realm of oncology, TNF-α plays a significant role in facilitating angiogenesis and promoting the survival of neoplastic cells, with a multitude of studies highlighting its upregulation as a detrimental prognostic indicator in breast cancer. The overlapping functionalities of TNF-α elucidate its elevated presence in both the milieu of autoimmune inflammation and the dynamics of tumor biology, thereby accounting for its robust correlation with chronicity observed within our cohort [21][22].

The concurrent elevation of IL-10 alongside TGF-β may initially appear paradoxical, yet it epitomizes the intricate and often compensatory dynamics inherent within cytokine networks. Both IL-10 and TGF-β assume pivotal regulatory functions that curb excessive inflammation characteristic of autoimmune disorders, while simultaneously fostering immune suppression and enabling tumor immune evasion within oncological contexts [23]. A plethora of reviews and meta-analyses elucidate this "double-edged" nature of IL-10, as well as the context-sensitive protumorigenic ramifications of TGF-β, which can promote epithelial–mesenchymal transition and metastatic dissemination, notwithstanding their anti-inflammatory properties . Hence, the heightened levels of anti-inflammatory cytokines observed in our patient cohort are likely indicative of both a feedback mechanism addressing the chronic inflammation seen in systemic lupus erythematosus (SLE) and the immunosuppressive microenvironments prevalent in breast cancer [24][25].

When analyzing sociodemographic factors, we see interesting patterns that the older the women are and higher BMI exist among breast cancer patients. This finding warrants investigation given elevated adiposity acts as the largest origin of interleukin-6 (IL-6)

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besides multiple other pro-inflammatory agents and may cause artifactual elevation towards systemic cytokine content irrespective of disease etiology. 37 Moreover, the so-called "inflammaging" (i.e., age-related changes in immune responsiveness) may also contribute to higher response of baseline cytokine production [26]. Hence, although the elevated concentrations in cytokine levels are likely a reflection of the underlying pathology, it is also important to recognize that some biological signal may be due to these host-related variables as well. Hence, performing multivariable adjustments in larger and more heterogeneous populations would be an important initiative to go forward with that aims to disentangle disease-specific from intrinsic host effects 27.

Taken as a whole, the sum of evidence accumulated in the course of this investigation supports the concept that both SLE and breast carcinoma may share common cytokine dysregulation; specifically, IL-6 and TNF-α are potential key mediators in both diseases, IL-10 and TGF-β define either regulatory or pro-tumorigenic roles or adaptations. Most of the variation with that was observed in current study would mainly be due to differences in the characteristics of cohorts, stages of disease development, assay methodologies and concurrent therapeutic treatments [29]. In future the necessity of longitudinal studies using standardized assays and accounting carefully for confounding variables such as BMI, age, and therapeutic regimens is mandatory to support the potential role of cytokine panels as reliable dual biomarkers that condition autoimmune activity progression into cancer 30.

Conclusion

Both pro-inflammatory and anti-inflammatory cytokines were significantly upregulated in patients suffering with SLE with or without breast cancer, which points towards high levels of immune activation. In SLE, these augmented cytokines are associated with disease duration, and thus can be attributed to chronic inflammation and tissue damage. In breast cancer, higher cytokine expressions have been correlated with the progression of the tumor because they are involved in remodeling tissue and stimulating angiogenesis or immune modulation in the TME. These data underscore the opposing nature of cytokines in mediating autoimmunity (in SLE) and E microenvironment-dependent malignancy generation (breast cancer), and the relevance they have in disease physiopathology. The results of our study emphasise that both pro and anti-inflammatory cytokines are involved in the pathogenesis to SLE as well as breast cancer. In SLE, the increased cytokine levels are associated to chronic inflammation and tissue damage, contributing towards disease progression in general. However, high levels of these cytokines in breast cancer tissue could have a role at least partly in tumour progression through re-modeling the tissue, neo-angiogenesis and immune modulation inside the tumor. Such findings show the paradoxical and complicated function of cytokines in autoimmune diseases and tumor development, indicating that they may serve as potential therapeutic targets for treatment. The therapeutic implications of cytokine modulation to control SLE as well as breast cancer remain open to further investigation in the future.

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