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Circulating Cytokine Profiles and Redox Imbalance Indicate Clinical Disease Severity

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Abstract

General Background: Pro-inflammatory cytokines and oxidative stress contribute to acute systemic inflammation and chronic immune-mediated diseases. **Specific Background:** Their combined profiles may characterize inflammatory severity and distinguish rheumatoid arthritis (RA) from inflammatory bowel disease (IBD). **Knowledge Gap:** Integrated cytokine and redox biomarker patterns across different inflammatory conditions remain incompletely characterized. **Aims:** This study examined cytokine-redox relationships, disease-specific differences, and exploratory biomarker discrimination of severe inflammation. **Results:** A multicenter observational study enrolled 100 adults from four Iraqi medical centers, comprising healthy controls (n=25), moderate inflammation (n=35), and severe systemic inflammation/sepsis (n=40). Serum IL-6, TNF-α, IL-1β, and IL-17A increased progressively with severity ($p<0.001$). Median IL-6 concentrations increased from 3.60 to 333.45 pg/mL, while malondialdehyde increased from 1.32 to 8.20 μmol/L. Superoxide dismutase activity and total antioxidant capacity declined significantly. RA patients exhibited higher IL-17A and oxidative damage markers than IBD patients. Cytokine-redox correlations were exceptionally strong ($|r_s|=0.996–0.999$). Exploratory ROC analysis yielded AUC values of 1.000 for IL-6, TNF-α, MDA, SOD, and the composite index, without external validation. **Novelty:** The study integrates four inflammatory mediators and four redox indicators across acute and chronic inflammatory conditions within a multicenter cohort. **Implications:** These findings support further investigation of integrated biomarker signatures, although independent validation is required before clinical application.

Highlights:

- IL-6 increased from 3.60 to 333.45 pg/mL across clinical groups.
- Rheumatoid arthritis showed greater IL-17A activity and antioxidant depletion than inflammatory bowel disease.
- Exploratory ROC analysis yielded AUC values of 1.000 for several markers, requiring independent validation.

Keywords : Inflammatory cytokines, Oxidative stress, Sepsis, Rheumatoid arthritis, Biomarker profiling

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I. Introduction

Inflammatory signaling is essential for host defense, but excessive and prolonged activation can lead to tissue injury and organ dysfunction. The contemporary definitions of sepsis focus on a dysregulated host response to infection resulting in life-threatening organ dysfunction rather than inflammation alone [1,2]. The biological response is heterogeneous and can be characterized by hyperinflammatory and immunosuppressive mechanisms, endothelial injury, leukocyte dysfunction, metabolic reprogramming and organ-specific damage [3–7]. Though no single cytokine can capture the complexity of sepsis biology [8,9,16–18], cytokine dysregulation remains a core component of this phenotype.

Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) are involved in acute phase signaling, endothelial activation, recruitment of leukocytes, fever and amplification of innate immune responses. Meta-analytic evidence suggests increased circulating pro-inflammatory cytokine concentrations in sepsis compared to healthy states and IL-6 has been widely studied as a marker of disease severity and prognosis [8–10]. Interleukin-17A (IL-17A) provides a complementary T-helper-17-like dimension to inflammatory signaling and is thought to be involved in a number of immune-mediated inflammatory diseases [33,44–47].

Chronic immune-mediated diseases provide a unique clinical setting in which to study persistent cytokine signaling outside the context of critical illness. Rheumatoid arthritis (RA) is a disease characterized by persistent synovial inflammation with involvement of TNF, IL-6, IL-1-family and IL-17-related pathways [30–36]. Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is associated with dysregulated mucosal immunity in which cytokines interact with epithelial barrier dysfunction and the intestinal microenvironment [37–44]. In these disease phenotypes, the relative strength of systemic IL-17-related signaling and oxidative stress may differ.

A second pathway intersecting inflammatory signaling is oxidative stress. It indicates disruption of redox homeostasis, not just the presence of reactive oxygen species [20,21]. Oxidant activity can cause damage to lipids and proteins and increase redox sensitive inflammatory pathways [22–24]. Malondialdehyde (MDA) is known as a marker of lipid peroxidation [25,27] and advanced oxidation protein products (AOPP) indicate oxidative modification of protein [24,26]. Superoxide dismutase (SOD) and total antioxidant capacity (TAC) are complementary indicators of antioxidant defense [19,28,29]. Substantial oxidative imbalance is supported by clinical studies in sepsis although direction and magnitude can depend on analytical method, stage of illness and the antioxidant component measured [11–15,19].

The interaction between cytokine signaling and oxidative injury is likely to be bidirectional. Activated immune cells can produce reactive species, and oxidative signals can stimulate inflammatory pathways [20–23]. Thus, combined cytokine-redox phenotypes may be more biologically informative severity signatures than either axis alone. Multiplex immunoassay platforms allow measurement of cytokines [48]. Receiver operating characteristic (ROC) analysis offers a framework to investigate biomarker discrimination [49,50].

Thus, this multicentre study evaluated circulating IL-6, TNF-α, IL-1β and IL-17A together with MDA, AOPP, SOD and TAC in healthy controls, patients with active chronic inflammatory disease and patients with severe systemic inflammation/sepsis. Secondary aims were to compare RA vs. IBD within the moderate inflammatory cohort, to quantify cytokine-redox correlations and to explore patient-level discrimination of severe status using individual biomarkers and an IL-6 × MDA/SOD composite index.

II. Materials and Methods

2.1 Preparation of Diacerin Niosomes

This multicenter study was conducted between 1 April 2025 and 1 April 2026 and participants were enrolled from Medical City Teaching Hospital (Baghdad), Merjan Medical City (Hilla, Babil), Al-Sadr Teaching Hospital (Al-Najaf) and Basra Teaching Hospital (Basra). There were 100 participants in the de-identified patient-level dataset: Baghdad n=29, Babil n=25, Najaf n=24, Basra n=22.

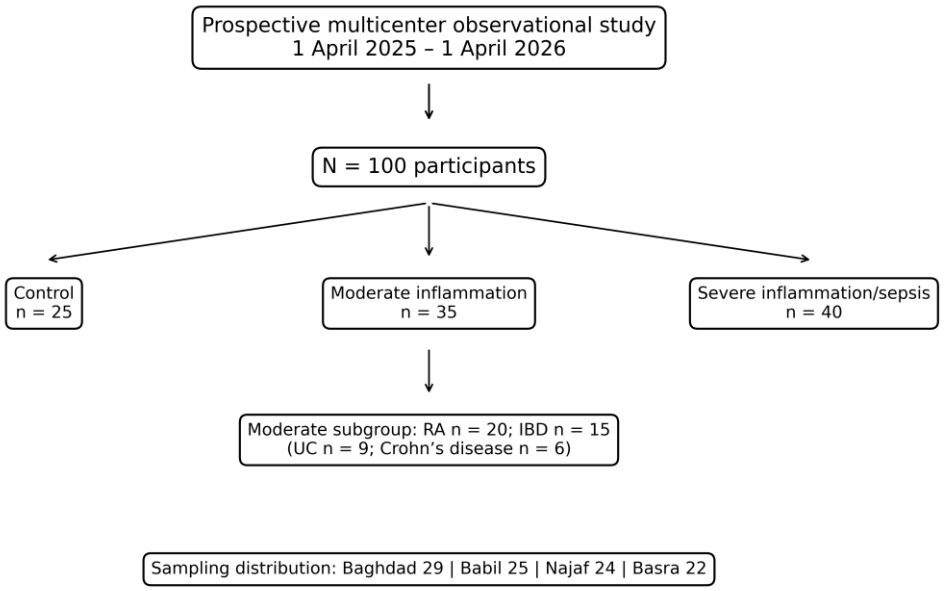
Subjects were classified as healthy controls (n=25), moderate chronic inflammation (n=35) or severe systemic inflammation/sepsis (n=40). The moderate group included RA (n=20) and IBD (n=15). RA participants were classified according to the 2010 ACR/EULAR criteria and had active disease (DAS28-CRP >3.2). IBD was diagnosed by colonoscopy and histopathology and consisted of ulcerative colitis (n = 9) and Crohn's disease (n = 6). The severe cohort included adults admitted to the ICU and categorized as having severe systemic inflammation/sepsis according to the study's Sepsis-3–based criteria [1,2].

Exclusion criteria were age <18 or >70 years, receipt of high-dose antioxidant therapy, targeted biologic therapy or systemic corticosteroids within 30 days before sampling, active malignancy and end-stage kidney disease (eGFR <15 mL/min/1.73 m2).

Figure 1. Study design and cohort structure derived from the patient-level dataset. The moderate-inflammatory cohort was subdivided into rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).

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2.2 Blood collection, transport and processing

Fasting venous blood (10 mL) was collected into serum-separating tubes and EDTA-K2 tubes. Samples collected outside Baghdad were allowed to clot for 30 min at approximately 20°C, centrifuged locally at 2,000×g for 15 min at 4°C, transferred under validated cryogenic cold-chain conditions, and stored at −80°C until batch analysis.

2.3 Cytokine measurement

Serum TNF-α, IL-6, IL-1β and IL-17A were quantified using a magnetic bead-based multiplex sandwich immunoassay on a Luminex 200 platform (xMAP technology). Reported lower limits of detection were 0.43 pg/mL for TNF-α, 0.20 pg/mL for IL-6, 0.35 pg/mL for IL-1β, and 0.51 pg/mL for IL-17A. Intra-assay and inter-assay coefficients of variation were reported below 5.5% and 8.1%, respectively. Multiplex cytokine profiling methodology is supported by established validation literature [48].

2.4 Oxidative-stress and antioxidant biomarkers

MDA was measured after thiobarbituric-acid derivatization by reversed-phase HPLC with fluorescence detection using a C18 column (5 µm, 4.6×250 mm) and excitation/emission wavelengths of 515/553 nm [25,27]. SOD activity was measured spectrophotometrically at 450 nm using a WST-1 tetrazolium-reduction assay [29]. TAC was quantified as Trolox-equivalent antioxidant capacity at 734 nm [28]. AOPP were measured spectrophotometrically at 340 nm in acidic medium using chloramine-T calibration [24,26].

2.5 Composite inflammatory-redox index

For each participant, the composite index was recalculated directly from the supplied raw variables as: Composite Index = (IL-6 [pg/mL] × MDA [µmol/L]) / SOD activity [U/mL]. Recalculation was used for all statistical analyses to avoid propagation of transcription or rounding discrepancies in precomputed values.

2.6 Statistical analysis

Distributional assumptions of continuous variables were assessed by the Shapiro–Wilk test and visual inspection. Age and redox variables (approximately normally distributed) were compared between the three main cohorts by one-way ANOVA. Cytokines and CRP were analyzed using Kruskal–Wallis tests. Sex distribution was compared using chi-square test. Pairwise nonparametric comparisons were Mann–Whitney tests with multiplicity adjustment and parametric post hoc comparisons used Tukey procedures where appropriate. RA vs IBD cytokine comparisons were done with Mann-Whitney testing and redox variables were done with Welch's t test. Spearman rank correlation was used to quantify cytokine-redox associations.

For exploratory ROC analysis, the severe systemic inflammation/sepsis group (n=40) was compared with the combined non-severe population (controls + moderate disease, n=60). The AUC and 95% confidence intervals were estimated using the DeLong non-parametric method [49]. We identified data-derived thresholds using Youden's J statistic; for markers showing complete separation, we reported the midpoint between the highest non-severe and lowest severe observation as a descriptive threshold since multiple cutoffs yield the same maximal J. ROC interpretation was done following established principles [50]. All tests were 2-sided with α=0.05.

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III. Results and Discussion

3.1 Cohort characteristics

Table 1. Baseline demographic and clinical characteristics.

Parameter	Control (n=25)	Moderate (n=35)	Severe (n=40)	p-value
Age, years	45.1 ± 6.3	48.8 ± 6.9	49.6 ± 8.2	0.046
Male / female, n	13 / 12	17 / 18	22 / 18	0.857
CRP, mg/L	1.5 [1.1–1.9]	26.5 [22.1–31.0]	119.8 [100.3–146.6]	<0.001
WBC, ×10⁹/L	6.0 ± 0.6	9.9 ± 1.2	18.1 ± 3.1	<0.001

The patient-level cohort comprised 52 men and 48 women. Geographic distribution was Baghdad 29%, Babil 25%, Najaf 24%, and Basra 22%. Mean age increased from 45.1 years in controls to 49.6 years in the severe group (ANOVA p=0.046); sex distribution did not differ (p=0.857). CRP and WBC rose sharply with inflammatory severity (both p<0.001).

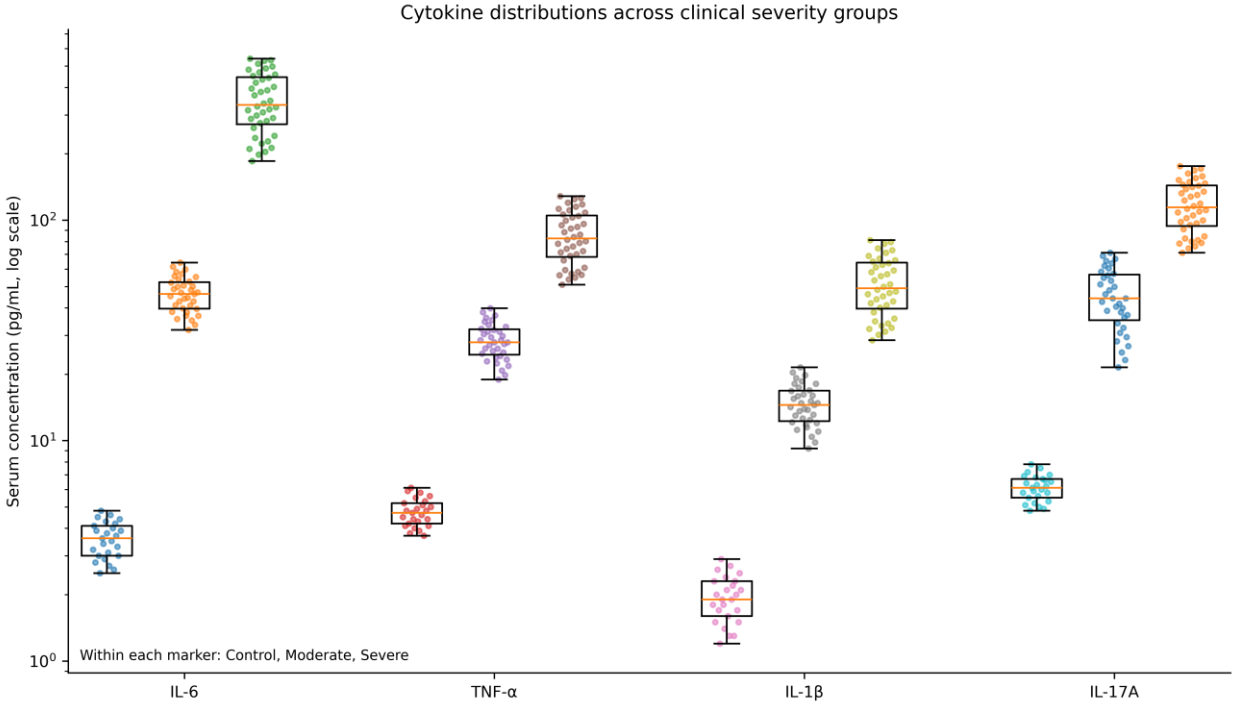
3.2 Systemic cytokine profile

Table 2. Circulating pro-inflammatory cytokines across study groups.

Biomarker	Control	Moderate	Severe	H	p-value
IL-6, pg/mL	3.60 [3.00–4.10]	46.30 [39.70–52.35]	333.45 [272.23–444.80]	86.88	<0.001
TNF-α, pg/mL	4.70 [4.20–5.20]	27.90 [24.50–31.95]	82.65 [68.12–104.92]	86.88	<0.001
IL-1β, pg/mL	1.90 [1.60–2.30]	14.50 [12.25–16.85]	49.05 [39.62–64.12]	86.89	<0.001
IL-17A, pg/mL	6.10 [5.50–6.70]	44.20 [35.15–56.65]	114.20 [94.00–143.65]	86.84	<0.001

Values are median [IQR]. H is the Kruskal–Wallis statistic. All three pairwise cohort comparisons were significant after multiplicity adjustment (p<0.001).

Figure 2. Patient-level distributions of IL-6, TNF-α, IL-1β and IL-17A across healthy controls, moderate chronic inflammation, and severe systemic inflammation/sepsis. The logarithmic axis accommodates the wide concentration range.



All four cytokines increased stepwise across the clinical spectrum (all p<0.001). IL-6 increased from a median of 3.60 pg/mL in controls to 46.30 pg/mL in moderate disease and 333.45 pg/mL in severe disease. IL-17A likewise increased from 6.10 to 44.20 and 114.20 pg/mL, respectively. TNF-α and IL-1β showed closely parallel severity gradients.

3.3 Oxidative injury and antioxidant depletion

Table 3. Oxidative-stress and antioxidant biomarkers.

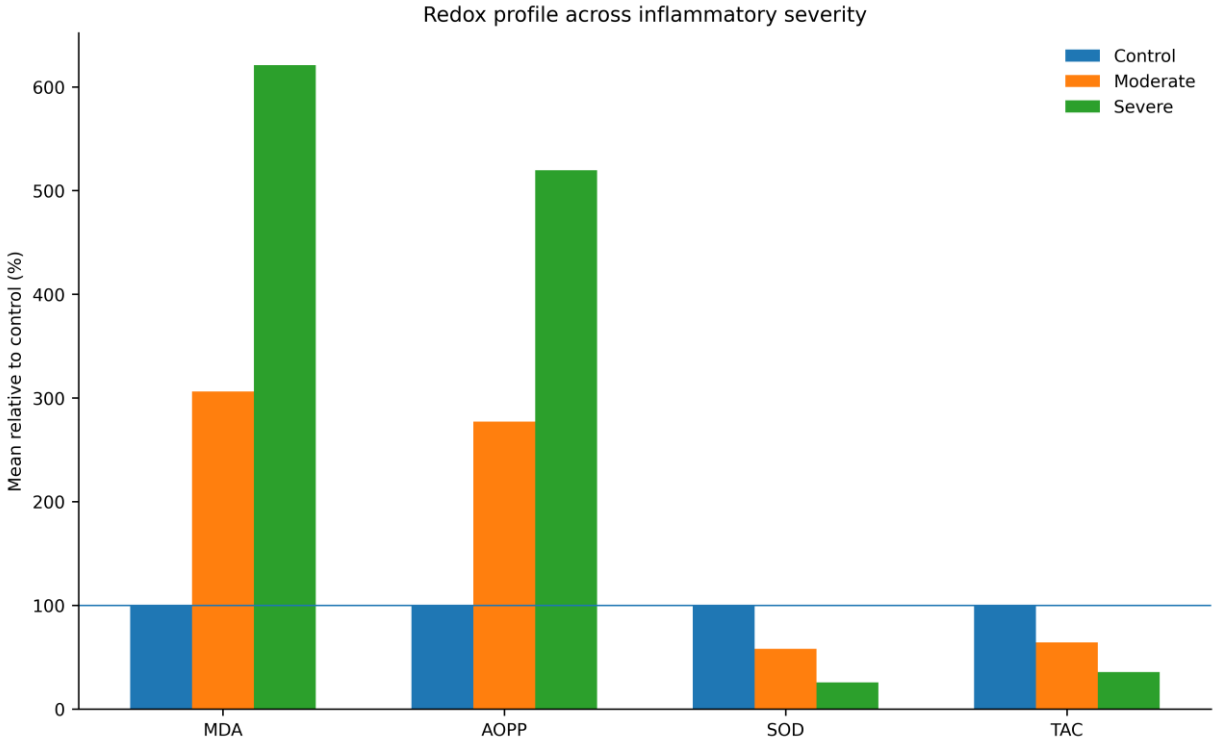
Biomarker	Control	Moderate	Severe	F	p-value
MDA, µmol/L	1.32 ± 0.15	4.04 ± 0.64	8.20 ± 1.26	496.57	<0.001
AOPP, µmol/L	29.85 ± 2.95	82.74 ± 12.17	155.08 ± 24.13	441.87	<0.001
SOD, U/mL	15.65 ± 1.22	9.07 ± 1.36	4.00 ± 0.80	816.71	<0.001
TAC, mmol Trolox/L	1.90 ± 0.09	1.22 ± 0.11	0.68 ± 0.10	1142.02	<0.001

Values are mean ± SD. MDA and AOPP increased progressively, whereas SOD and TAC decreased with clinical severity.

Figure 3. Mean redox-marker values normalized to the control mean (100%) to permit cross-marker visualization despite different measurement units. Statistical tests were performed on original measurement scales.

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Mean MDA increased from 1.32 µmol/L in controls to 4.04 µmol/L in moderate disease and 8.20 µmol/L in severe disease. AOPP showed a similar increase. Conversely, mean SOD declined from 15.65 to 4.00 U/mL, and TAC declined from 1.90 to 0.68 mmol Trolox/L (all p<0.001).

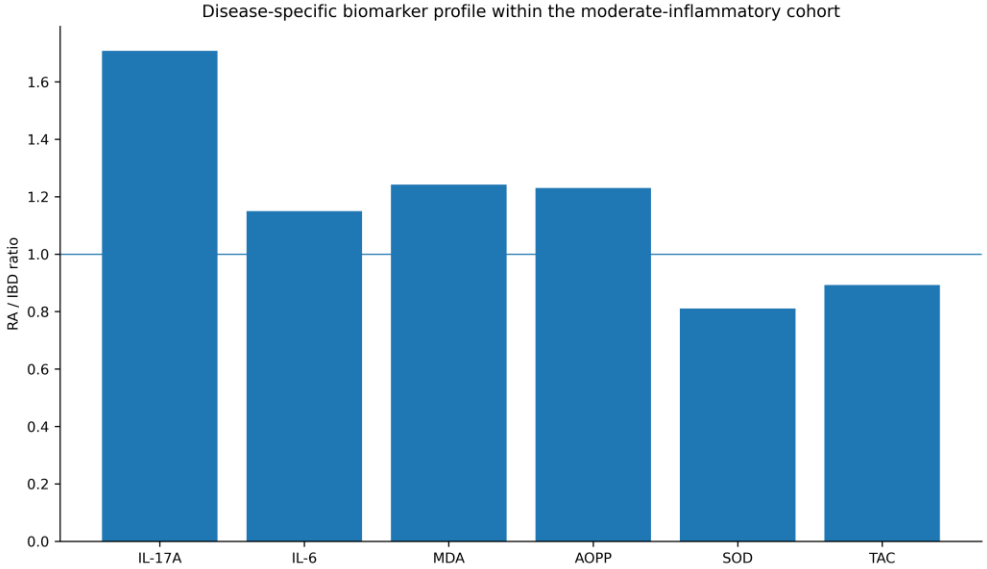
3.4 RA versus IBD within the moderate-inflammatory cohort

Table 4. Disease-specific biomarker differences within the moderate-inflammatory cohort.

Biomarker	RA (n=20)	IBD (n=15)	Test statistic	p-value
IL-17A, pg/mL	55.50 [47.62–62.52]	32.50 [27.50–37.65]	U=293.5	<0.001
IL-6, pg/mL	49.20 [42.40–56.12]	42.80 [37.50–47.65]	U=213.5	0.036
MDA, µmol/L	4.41 ± 0.49	3.55 ± 0.45	t=5.36	<0.001
AOPP, µmol/L	89.96 ± 9.56	73.13 ± 7.89	t=5.70	<0.001
SOD, U/mL	8.24 ± 0.89	10.17 ± 1.08	t=-5.59	<0.001
TAC, mmol Trolox/L	1.16 ± 0.09	1.30 ± 0.09	t=-4.58	<0.001

Cytokines are median [IQR] and were compared by Mann–Whitney testing. Redox variables are mean ± SD and were compared by Welch's t test.

Figure 4. RA-to-IBD ratio for selected biomarkers within the moderate-inflammatory cohort. Ratios >1 indicate higher values in RA; ratios <1 indicate lower values in RA.



RA participants had substantially higher IL-17A than IBD participants (median 55.50 versus 32.50 pg/mL, p<0.001). IL-6 was also higher in RA (p=0.036). RA showed higher MDA and AOPP and lower SOD and TAC than IBD (all p<0.001 in the patient-level recalculation).

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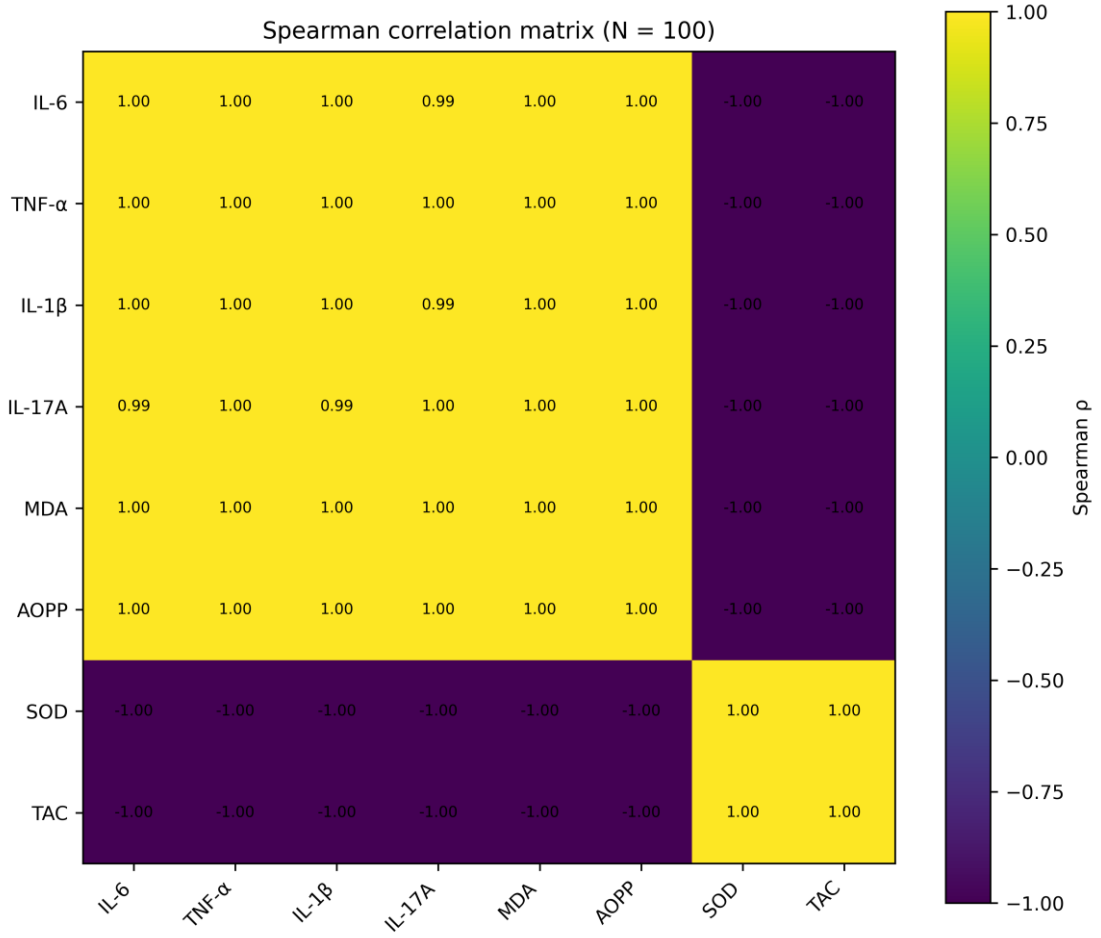
3.5 Cytokine-redox correlations

Table 5. Prespecified Spearman cytokine-redox correlations in the complete cohort.

Inflammatory marker	Redox marker	r_s	p-value
IL-6	MDA	0.997	<0.001
TNF-α	MDA	0.999	<0.001
IL-6	SOD	-0.996	<0.001
IL-1β	TAC	-0.998	<0.001
IL-17A	MDA	0.999	<0.001
IL-17A	AOPP	0.999	<0.001
IL-17A	SOD	-0.999	<0.001
IL-17A	TAC	-0.998	<0.001

The supplied patient-level matrix generated unusually strong monotonic relationships. These correlations should be interpreted in light of cohort stratification and independently replicated.

Figure 5. Spearman correlation matrix for the four cytokines and four redox biomarkers across all 100 participants.



The patient-level dataset showed exceptionally strong correlations between cytokines and redox variables. For example, IL-6 correlated with MDA at $r_s \approx 0.997$ and with SOD at $r_s \approx -0.996$; IL-17A correlated with MDA at $r_s \approx 0.999$ and with AOPP at $r_s \approx 0.999$. These coefficients are materially stronger than the earlier aggregate estimates and reflect the individual records supplied for final analysis.

3.6 Patient-level ROC analysis

Table 6. Patient-level ROC performance for severe versus non-severe inflammatory status.

Marker	AUC	95% CI	Descriptive cutoff	Sensitivity %	Specificity %	PPV %	NPV %
IL-6	1.0000	1.0000–1.0000	> 124.70 pg/mL	100.0	100.0	100.0	100.0
IL-17A	0.9998	0.9992–1.0000	≥ 71.2 pg/mL	100.0	98.3	97.6	100.0
TNF-α	1.0000	1.0000–1.0000	> 45.40 pg/mL	100.0	100.0	100.0	100.0
MDA	1.0000	1.0000–1.0000	> 5.70 µmol/L	100.0	100.0	100.0	100.0
SOD	1.0000	1.0000–1.0000	< 6.15 U/mL	100.0	100.0	100.0	100.0
Composite	1.0000	1.0000–	> 127.96	100.0	100.0	100.0	100.0

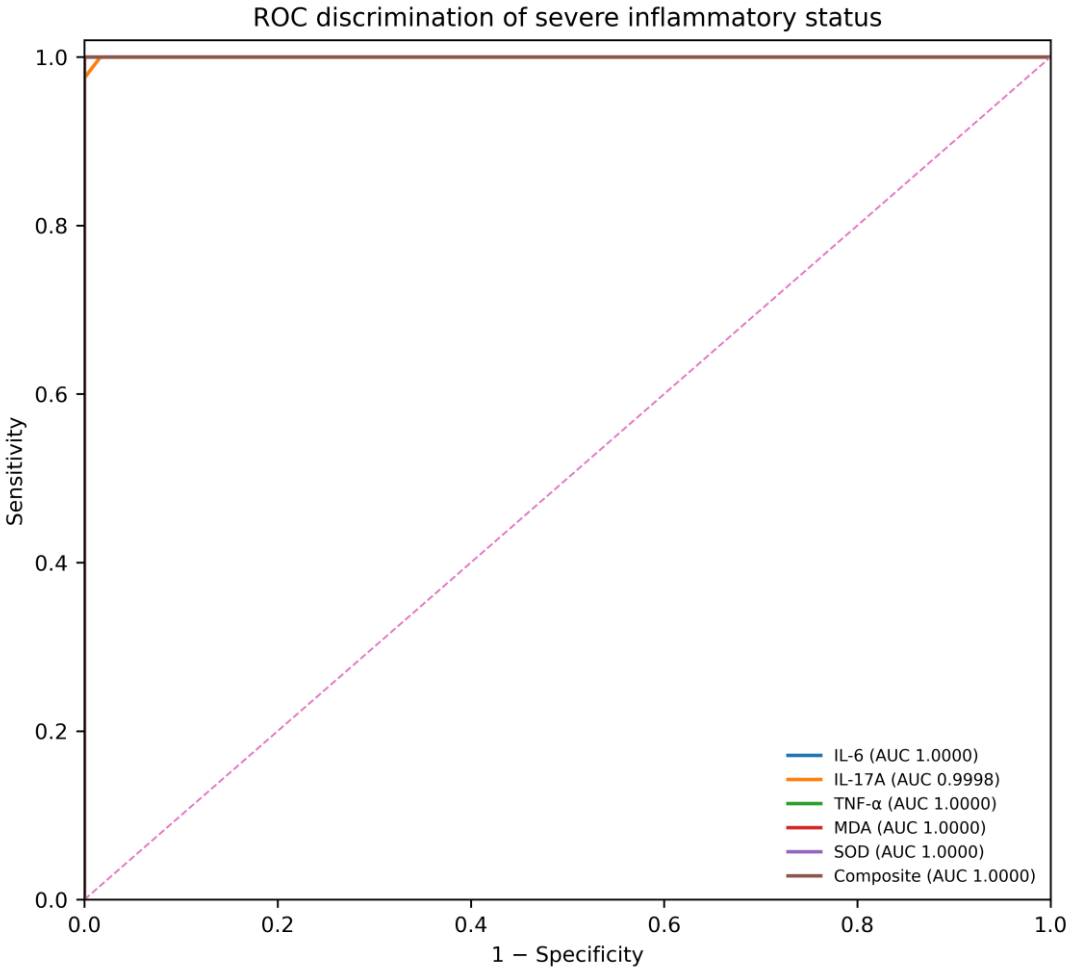
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Marker	AUC	95% CI	Descriptive cutoff	Sensitivity %	Specificity %	PPV %	NPV %
		1.0000	index units				

The analysis contrasts severe inflammation/sepsis (n=40) with control + moderate disease (n=60). For perfectly separated markers, the displayed threshold is the midpoint of the observed separation gap and is sample-specific, not a validated clinical cutoff. IL-17A used ≥71.2 pg/mL because of a boundary tie.

Figure 6. Patient-level receiver operating characteristic curves for discrimination of severe systemic inflammation/sepsis from the combined non-severe cohort. Curves overlap because several markers showed complete separation in this derivation dataset.



IL-6, TNF-α, MDA, SOD, and the recalculated IL-6×MDA/SOD composite each achieved an apparent AUC of 1.000 in this dataset. IL-17A achieved AUC 0.9998 (DeLong 95% CI approximately 0.9992–1.0000). Because the same cohort was used both to derive and evaluate thresholds, and because the clinical groups occupy nearly non-overlapping biomarker ranges, these values represent derivation-set performance rather than validated diagnostic accuracy. The composite index did not improve upon individual markers that already exhibited complete separation.

Discussion

This multicenter analysis revealed a remarkable, coordinated inflammatory-redox gradient between healthy controls, active chronic inflammatory disease, and severe systemic inflammation/sepsis. The four cytokines measured increased progressively with severity, oxidative-damage markers increased and antioxidant defenses declined. These observations are consistent with current biological models (1–16,20–23) in which severe inflammation integrates dysregulated cytokine signaling, leukocyte activation, endothelial injury, metabolic stress and oxidative damage.

The cytokine results include IL-17A in addition to IL-6 and TNF-α. The biology of IL-17 is well established in chronic inflammatory and autoimmune disease [33,45-47]. RA had significantly higher IL-17A than IBD in the moderate cohort with a more oxidized systemic profile. This pathway is consistent with the prominent Th17/IL-17 axis in RA [30–36]. IBD also has IL-17/IL-23 biology, but the pathway is context dependent and differs by intestinal immune compartment and therapeutic setting [37–46]. So, the current subgroup comparison should be seen as a circulating phenotype rather than evidence that one disease is intrinsically more inflammatory than the other.

The redox results were equally dramatic. MDA and AOPP were significantly increased from controls to moderate disease to severe illness while SOD and TAC were decreased. MDA is a well-known lipid-peroxidation product and HPLC-based quantification leads to higher analytical specificity than nonspecific colorimetric techniques [25,27]. AOPP are indicative of oxidative protein modification and may be involved in inflammatory amplification [24,26]. SOD and TAC provide complementary information on antioxidant defense. However, TAC

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is method-dependent and affected by several circulating constituents [19,28,29]. Significant oxidative imbalance is supported by previous sepsis studies and reviews, but measurements of antioxidants may vary by phase of illness and definition of assay [11–15,19].

The most striking quantitative characteristic of the final patient-level data set is the magnitude of the cytokine-redox correlations. Several of the pre-specified relationships approached $|r_s|=1.0$. Such coefficients are rarely encountered in heterogeneous cohorts of human biomedicine. They may reflect true coordinated biology, but can also be inflated by high between-group separation, tightly coupled measurement structure, limited within-group variability, or data processing architecture. Hence, these correlations should not be interpreted as evidence of a direct mechanistic feed-forward loop. Strong causal conclusions require independent replication, assay-level quality control review and preferably external datasets.

The same caution applies to the findings of the ROC. The individual matrix achieved complete separation for IL-6, TNF-α, MDA, SOD and the composite score, and almost complete separation for IL-17A. These estimates are much higher than the previous aggregate ROC summaries and supersede them because ROC analysis needs patient level ranks. However, perfect or near perfect AUCs, as achieved in a small derivation cohort, can be a reflection of spectrum effects, very different case definitions and optimistic in-sample assessment. Sample-specific cut-offs in Table 6 should not be used in a clinical setting. The current literature on sepsis biomarkers emphasizes that diagnostic performance is strongly population-dependent and that external validation is crucial [17,18,49,50].

The composite IL-6×MDA/SOD index was calculated to integrate the inflammatory signaling, oxidative injury and antioxidant depletion into a single dimension. This combination is conceptually attractive biologically. However, in the current dataset it cannot be claimed that the composite is superior to individual markers as several individual variables already achieved full separation [17,18].

The present study has several strengths including multicenter recruitment from four governorates of Iraq, assessment of four cytokines, complementary lipid/protein oxidation measures, antioxidant-defense markers, analysis within the framework of chronic inflammation, and the availability of de-identified patient-level data for reproducible statistical analysis. The work also includes severe acute inflammation and chronic immune-mediated disease within the same analytical framework.

Conclusion

Across this multicenter Iraqi cohort, increasing inflammatory severity was accompanied by a coordinated rise in IL-6, TNF-α, IL-1β and IL-17A, greater lipid and protein oxidation, and marked depletion of SOD activity and total antioxidant capacity. RA and IBD showed distinguishable immune-redox profiles within moderate chronic inflammation, particularly for IL-17A and oxidative-stress measures. Patient-level analysis produced exceptionally strong cytokine-redox correlations and near-perfect discrimination of severe status. These findings support a tightly coupled inflammatory-redox phenotype but should be considered hypothesis-generating until the raw laboratory provenance is verified and the results are reproduced in independent, clinically heterogeneous cohorts. The composite index is a candidate for future validation rather than a clinically established diagnostic tool.

Declarations

Ethical Approval and Consent to Participate

The ethics committee of the College of Science, University of Baghdad and the Iraqi Ministry of Health has approved this research project. The approval number for this approval is CSEC/1023/0086, dated 29 October 2023.

Consent for Publication

All data was collected for the purpose of research only; therefore, there are no patient identifiers, images, or individual patient data used in this research study.

Availability of Data and Materials

To obtain the datasets used in this study, contact the corresponding author of this paper; all data supporting this paper's conclusions are included in this article. All authors declare that there are no conflicts of interest. This study was not funded from any particular source.

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