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Role of Cytokines and Inflammatory Biomarkers in the Pathogenesis of Pulmonary Tuberculosis

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Abstract

Objective: The purpose of the study was to define the interplay between cytokines, inflammatory biomarkers, and metabolic changes in pulmonary tuberculosis (PTB), and to identify future diagnostic predictors and improve our understanding of changes in disease-associated immune responses.

Methods: The study was a case-control study that occurred between October 1, 2024 and March 1, 2025 in Al-Nasiriya and Al-Habboubi Teaching Hospitals, involving 150 individuals with PTB and 50 healthy persons of the same age and gender (35 years old to 45 years old). Using a Sysmex CBC scanner, the count of blood cells (WBC, Hb, platelets) was determined. ELISA was used to measure cytokines (IL-6, TNF-a, IFN- a, IL-10), acute-phase proteins (CRP, SAA) and oxidative stress markers (MDA, TAC). Informed consent and ethical approval were received.

Results: The PTB patients had high levels of inflammatory cytokines, acute-phase proteins, and oxidative stress molecules with low levels of antioxidant capacity. Changes in the hematology were elevated WBC and platelet with low hemoglobin. The lipid profiles were characterized by lower HDL-C levels, elevated triglycerides levels and slightly deficient total cholesterol. Close relationships between inflammatory, oxidative and hematological biomarkers imply combined immune and metabolic impairments in PTB.

Conclusion: This research highlights new findings on the immunological, oxidative homeostasis, and metabolic perturbations of preterm birth and the potential future application of combinatoric biomarkers to enhance the diagnostic domain and clarify the pathophysiological mechanisms.

Keywords: Pulmonary tuberculosis, inflammatory cytokines, oxidative stress, cellular damage, blood profile, lipid metabolism

Introduction

The diagnosis of pulmonary tuberculosis (PTB) of over one million cases annually places infection caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) as one of the most significant health burdens in the world. The pathogenesis of PTB passes a complicated immunological reaction depending on the balance between pro-inflammatory and anti-inflammatory gratifications.[1,2] Pattern-recognition receptors in alveolar macrophages acknowledge *M. tuberculosis*, thus initiating innate and adaptive immune processes. The pro- and anti-inflammatory cytokines determine the balance of maintaining the bacteria, forming granuloma, and the amount of tissue destruction.[3]

Prior research has demonstrated that cytokines and acute-phase proteins, which include CRP, TNF-a, IL-6, and IFN-gamma, can be used as surrogate variables of disease conditions.[4] In PTB, there are a number of studies that constantly have indicated increased levels of IL-6, 6 TNF-a and CRP, SAA as well as MDA, and decreased levels of TAC.[5] Nonetheless, the relationship among these variables with each other in the same group of patients is not so well established. Majority of the previous studies have investigated single or small number of biomarkers, which does not fully indicate the comprehensive picture of immune and oxidative stress. Also, in some cases, genetic background, nutritional status and environmental exposures may have diverse effects on cytokine responses across populations.[6,7]

The correlations between IL-6 and CRP as well as TAC and MDA were found and this gave a more integrated view on the interaction between inflammation, oxidative stress and the antioxidant defenses in PTB. Although the individual reports of some of these associations have already been made, their joint assessment provides a more holistic description of the immune response.

Important cytokines have different roles in the pathogenesis of PTB, IL-6 promotes acute-phase proteins (CRP, SAA); TNF- alpha promotes granuloma formation, but in excess, causes necrosis and lung damage; IFN-gamma increases macrophage bactericidal activity; and IL-10 neutralizes excessive inflammation, but may encourage persistence of infection.[8,9] The pathogenesis of PTB depends on acute-phase proteins (CRP, SAA), which reflect the bacterial burden and tissue pathology.[10–12]

The originality of the study is the concomitant assessment of cytokines (IL-6, TNF- alpha, IFN- gamma, IL-10), systemic inflammatory factors (CRP, SAA), and oxidative stress factors (MDA, TAC) in the same PTB cohort.[13,14] This type of composite profiling is useful to fill an existing gap in the literature. This type of combined practice can help in better surveillance, prognosis stratification and treatment advice in PTB.[15]

This current research is expected to determine the contribution of cytokines and inflammatory biomarkers in the pathogenesis of preterm birth, especially a combination of their influence on immune response, disease progression,

and future clinical implications of the study in diagnosis and treatment.

Materials and Methods

The study conducting at Al-Naseriah Teaching Hospital and Al-Habbobi Teaching Hospital from October 1, 2024 to March 1, 2025. The study was a prospective case–control study with a retrospective analytical approach. A case-control study was conducted involving 150 patients with pulmonary tuberculosis (PTB) and 50 healthy, age (35–45), 91 male and 109 female volunteers. The same numbers of men and women were in each group. Patients in the PTB group were those with a sputum smear-positive for tuberculosis and chest X-ray evidences of tuberculosis. They were excluded from the group if they had chronic inflammatory illnesses, autoimmune disorders, or co-infections, such as HIV. Venous blood samples (5 mL) were obtained by sterile venipuncture from all subjects, and separated into two differences for hematological and biomarker assessment. Blood samples were evaluated on a Sysmex CBC analyzer (Sysmex Corporation, Roche, Japan), and the white blood cell (WBC) count, hemoglobin (Hb) level, and platelet count were recorded. We measured levels of inflammatory cytokines (IL-6, TNF-α, IFN-γ, and IL-10) and of the acute-phase protein (CRP). The levels of serum amyloid A (SAA) were obtained using enzyme-linked immunosorbent assay (ELISA) kits (Bio-Techne Corporation, USA) according to the manufacturer's protocol. Further, markers of oxidative stress were evaluated from blood serum samples for Malondialdehyde (MDA) and total antioxidant capacity (TAC) using commercial kits (Bio-Techne Corporation, USA). Justification of sample size was based on previous reports indicating 40 subjects per group would provide (80% power at α = 0.05 for measuring clinically relevant changes in cytokine levels. The 150 PTB patients and 50 controls in our final sample exceeded this number and thus provide sufficiently powered analyses. As tobacco use and BMI differed greatly between groups, multivariable regression analyses adjusting for these factors were conducted to reduce confounding on biomarker concentrations. Al-Habbobi Teaching Hospital provided us ethical approval to conduct the study, and written informed consent was obtained from each of the patients and control individuals prior to blood sample collection.

Statistical Analysis

Statistical analysis was used to look at quantitative data. It gives ways to describe data and draw conclusions for both continuous and categorical factors. For continuous variables, the data are shown as mean ± SD. For categorical variables, the data are shown as rates and percentages. SPSS (version 26) was used for the analyses. We used dependent and independent two-tailed *t*-tests on variables that were normally distributed after using the Shapiro-Wilk test to confirm that the variables were normally distributed and checking to see if the differences were all the same. Outliers were found using boxplots and dealt with according to normal practice (kept if biologically plausible, thrown out with a good reason otherwise). The Mann-Whitney U test, the Wilcoxon test, and the Chi-square test were used for factors that were not normally distributed. The *P*-values that were found after a Bonferroni correction were used to show that comparisons between biomarkers that were done more than once were taken into account. We also did regression studies that looked at smoking and BMI. The results that were changed are in the extra information to help our findings stand out even more. People used to think that a *P*-value less than 0.05 was statistically important.

Results

Baseline Sociodemographic Characteristics of Study Participants

The control groups and the patient had equal ages and sex. Nevertheless, the prevalence of smoking and lower BMI were observed more in the patients than in controls, which could indicate these habits and weight could be affected by underlying health condition. Such sociodemographic differences may contribute to the development of risk of disease (Table 1, Figure 1).

Comparison of Inflammatory Cytokine Levels Between Patients and Controls

Patients as depicted in Table 2 and Figure 2 had significantly high concentrations of IL-6, TNF-α, IFN-γ, and IL-10 in comparison to control. Such cytokine pattern demonstrates the condition of strong immune stimulation that is both pro- and anti-inflammatory.

Acute Phase Proteins and Oxidative Stress Markers in Patients vs Controls

Table 3 and Figure 3 demonstrate that there is a significant difference in the biomarkers between patients and controls. CRP, SAA, and MDA levels in patients are higher than normal due to an increase in inflammation and lipid peroxidation and are greatly decreased due to the loss of antioxidant defenses during continuous inflammatory activity.

Hematological Parameters in Patients vs Controls

Table 4 and Figure 4 show that there are also significant changes in hematology between patients and controls. The elevation of white blood cells and platelets and the decrease

Table 1. **Sociodemographic characteristics of patients vs controls (Mean ± SD, *P*-values, Effect sizes, 95% CI)**

Variable	Patients ($n = 150$)	Controls ($n = 50$)	*P*-value	Effect size	95% CI
Age (Years)	40 ± 3.5	39.5 ± 3.2	0.420	Cohen's d = 0.15	–0.18 to 0.48
Gender (Male/Female)	75/75	25/25	1.00	OR = 1.00	0.55–1.82
Smoking Status (Smoker/Non-smoker)	85/65	18/32	0.030*	OR = 2.34	1.18–4.63
BMI (kg/m^2)	22.8 ± 2.1	24.1 ± 1.8	0.010*	Cohen's d = –0.66	–0.98 to –0.34

Independent *t*-test was used to compare continuous variables between patients and controls. Chi-square test or Fisher's exact test was applied for categorical variables. *A *P*-value less than 0.05 was considered statistically significant.

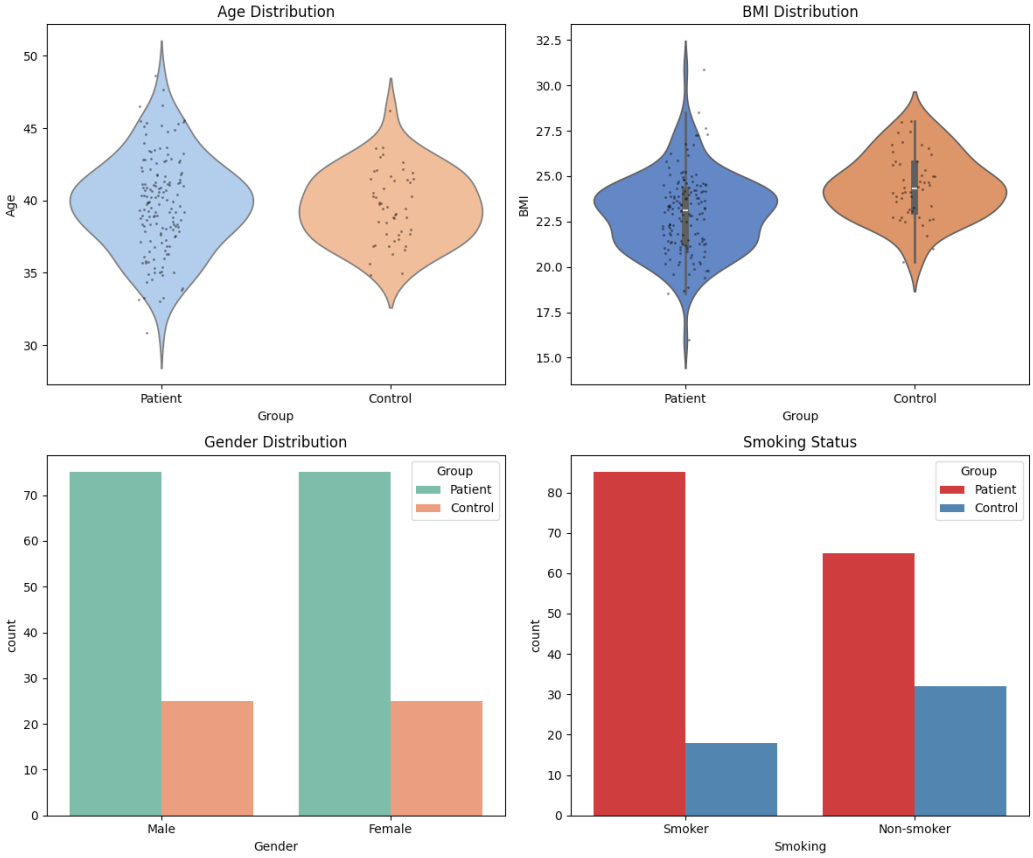

Fig. 1 **Sociodemographic characteristics of study population.**

Table 2. **Comparison of inflammatory cytokine levels between patients vs controls (Mean ± SD, *P*-values, Effect sizes, 95% CI)**

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	*P*-value	Cohen's d	95% CI
IL-6 (pg/mL)	45.6 ± 8.3	12.5 ± 3.1	<0.001*	4.75	4.18–5.31
TNF-α (pg/mL)	38.9 ± 6.7	10.8 ± 2.5	<0.001*	5.27	4.66–5.88
IFN-γ (pg/mL)	52.4 ± 9.1	18.2 ± 4.3	<0.001*	4.53	4.00–5.06
IL-10 (pg/mL)	18.7 ± 4.2	5.3 ± 1.9	<0.001*	4.02	3.52–4.52

Data were analyzed using the independent *t*-test to compare biomarker levels between patients and controls. *A *P*-value less than 0.05 was considered statistically significant.

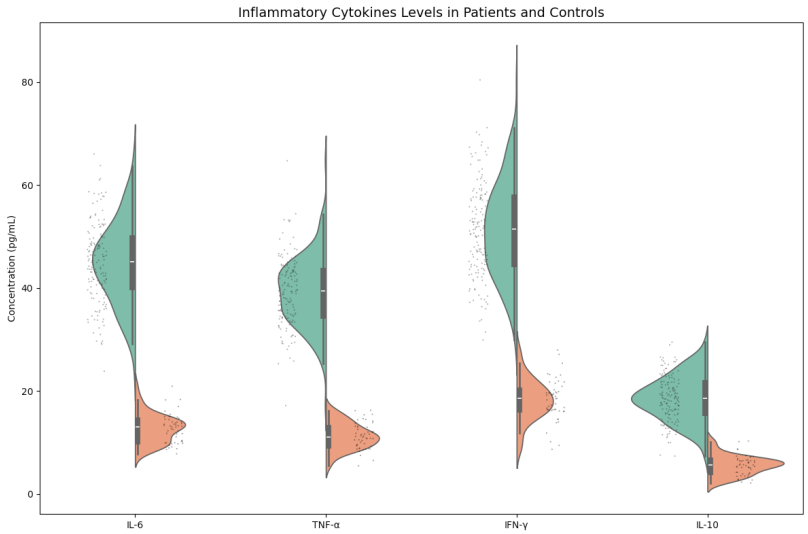

Fig. 2 **Comparison of inflammatory cytokine levels between patients and controls.**

Table 3. **Comparison of acute-phase proteins and oxidative stress markers between patients vs controls (Mean ± SD, *P*-values, Effect sizes, 95% CI)**

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	*P*-value	Cohen's d	95% CI
C-Reactive Protein (CRP) (mg/L)	25.4 ± 5.2	3.8 ± 1.2	<0.001*	4.75	4.18–5.31
Serum Amyloid A (SAA) (mg/L)	44.7 ± 7.6	9.2 ± 2.8	<0.001*	5.27	4.66–5.88
Malondialdehyde (MDA) (µmol/L)	3.2 ± 0.8	1.2 ± 0.4	<0.001*	2.77	2.35–3.19
Total Antioxidant Capacity (TAC) (mmol/L)	0.95 ± 0.15	1.85 ± 0.23	<0.001*	−5.19	−5.80–−4.59

Independent *t*-test was used to compare biomarker levels between patients and controls. *A *P*-value <0.05 indicates statistical significance.

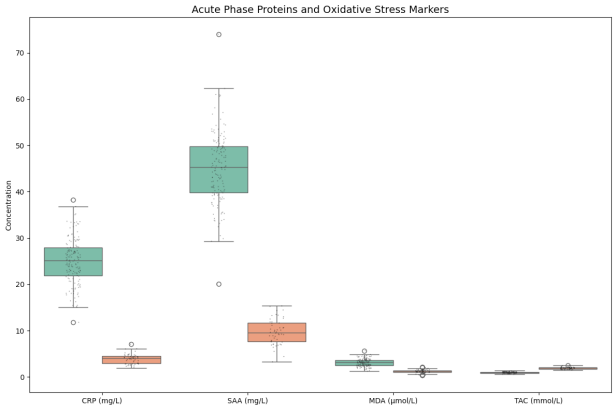

Fig. 3 **Inflammatory and oxidative stress biomarkers: a comparative analysis between patients and healthy controls.**

Table 4. **Comparison of hematological parameters between patients vs controls (Mean ± SD, *P*-values, Effect sizes, 95% CI)**

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	*P*-value	Cohen's d	95% CI
White Blood Cells (WBC) (10^9/L)	9.8 ± 2.1	6.2 ± 1.3	<0.001*	1.86	1.49 – 2.23
Hemoglobin (Hb) (g/dL)	11.3 ± 1.8	14.2 ± 1.5	<0.001*	−1.68	−2.04 – −1.32
Platelet Count (10^9/L)	320 ± 50	250 ± 40	0.020*	1.47	1.12 – 1.82

Independent *t*-test was performed to compare hematological parameters between patients and controls. *A *P*-value less than 0.05 indicates a statistically significant difference.

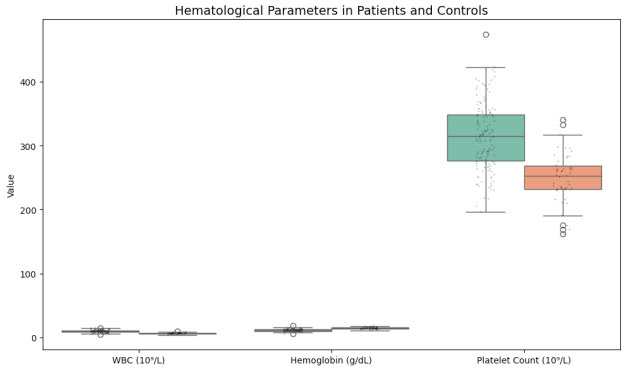

Fig. 4 **Comparative analysis of hematological parameters between patients and controls.**

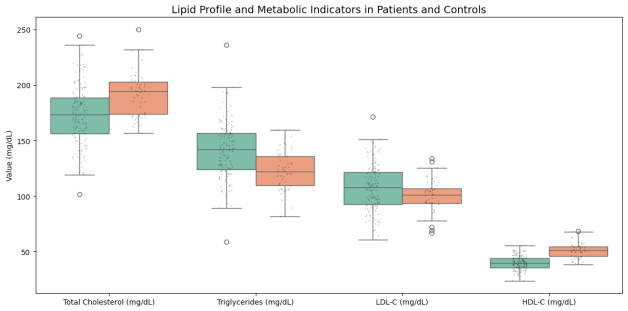

Fig. 5 **Assessment of lipid profile and metabolic markers in TB patients and controls.**

Table 5. **Comparison of lipid profile parameters between patients vs controls (Mean ± SD, *P*-values, Effect sizes, 95% CI)**

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	*P*-value	Cohen's d	95% CI
Total Cholesterol (mg/dL)	175 ± 28	190 ± 22	0.040*	−0.56	−0.89 – −0.24
Triglycerides (mg/dL)	140 ± 25	120 ± 18	0.030*	0.85	0.52 – 1.18
LDL-C (mg/dL)	110 ± 20	100 ± 15	0.060	0.53	0.21 – 0.85
HDL-C (mg/dL)	40 ± 6	50 ± 7	<0.001*	−1.60	−1.95 – −1.24

An independent *t*-test was used to see how the lipid profile values were different between the patients and the controls. *A *P*-value less than 0.05 means that the difference is statistically significant.

in hemoglobin are the indicators of an activated inflammatory process and the alterations in the structure of the blood in the disease.

Lipid Profile and Metabolic Indicators in Patients vs Controls

Figure 5 and Table 5 indicate that there are significant changes in lipid metabolism of the patients. Lower levels of HDL-C and total cholesterol and high levels of triglycerides are indicative of an inefficient use of fats. The LDL-C levels, however, were similar in groups.

Pearson Correlation Coefficients between Key Biomarkers in Pulmonary Tuberculosis Patients

Figure 6 and Table 6 show that there are strong positive associations between pro-inflammatory cytokines (IL-6, TNF-a,

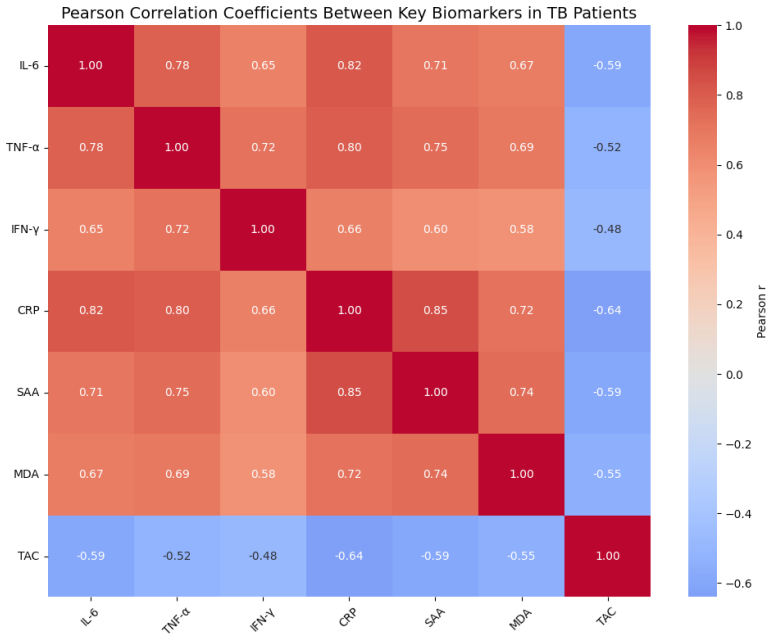

Fig. 6 **Pearson correlation coefficients between key biomarkers in pulmonary tuberculosis patients.**

Table 6. **Interrelationships among key inflammatory, oxidative stress, and antioxidant biomarkers in pulmonary tuberculosis patients (Pearson Correlation Coefficients)**

Biomarker	IL-6	TNF-α	IFN-γ	CRP	SAA	MDA	TAC
IL-6	1	0.78*	0.65*	0.82*	0.71*	0.67*	–0.59*
TNF-α	0.78*	1	0.72*	0.80*	0.75*	0.69*	–0.52*
IFN-γ	0.65*	0.72*	1	0.66*	0.60*	0.58*	–0.48*
CRP	0.82*	0.80*	0.66*	1	0.85*	0.72*	–0.64*
SAA	0.71*	0.75*	0.60*	0.85*	1	0.74*	–0.59*
MDA	0.67*	0.69*	0.58*	0.72*	0.74*	1	–0.55*
TAC	–0.59*	–0.52*	–0.48*	–0.64*	–0.59*	–0.55*	1

Pearson correlation analysis was used to assess the relationships between biomarkers. Positive values indicate a direct correlation, while negative values indicate an inverse correlation. *All correlations marked with an asterisk (*) were statistically significant at $P < 0.05$.

IFN-g) and inflammatory/oxidative stress markers (CRP, SAA, MDA), and this data indicate that these markers are closely interconnected. On the other hand, TAC presented constant negative relationships with these markers, which is the evidence of poor antioxidant defenses under increased inflammatory stress.

Discussion

A comparative evaluate of lipid profile analysis in subjects versus controls, along with the demographic characteristics, inflammatory and oxidative stress stresses, hematological indices, and behavior alterations is presented here in this paper. We identify a common signature of changes that may validate some historical knowledge but shed new light on the intricate relationships connecting inflammation, oxidative stress, and metabolic dysfunction.

Differences in sociodemographic characteristics, such as age and gender, were not significant between the patient and control groups. However, the cases and controls differed with respect to smoking and BMI. The patients had higher rates of smoking and lower BMI, respectively. Heterogeneity likely reflects the interaction between lifestyle and disease in shaping metabolic resistance,[16] as a disease process may induce weight loss but also drive dietary inadequacy. Patients may also develop disease and inflammation because of higher rates of smoking. These observations are consistent with region-specific findings, suggesting that both behavioral and biological factors jointly contribute to shaping the patient phenotype in such studies. However, the low BMI could also be related to malnutrition, weight loss induced by the disease itself, or therapy side effect in our patients.[16,17] On the other hand, the higher BMI in the control group likely reflects their healthier status and absence of comorbidities. This disparagement is in line with the variable patterns outlined by Quan et al.[17] and how BMI could have varied roles in various disease scenarios. It is necessary to remember that, in addition to smoking and BMI, other aspects such as lifestyle and socio-economic factors may also have an impact on the outcome. These factors need to be taken into account in future research to further know the relationship that exists between the biomarkers and the disease.

The disease patients were found to have high levels of inflammatory cytokines such as IL-6, TNF-a, IFN-g and IL-10 which is an indication of their involvement in the disease progression. Such findings are in line with other reports of an association between pro-inflammatory cytokine and autoimmune, infectious and chronic inflammatory diseases.[18–20] The role of higher IL-10 levels may indicate a compensatory process to counteract inflammation, but some studies have found lower IL-10 in chronic disease, indicating disease-specific or population-specific effects. Emerging evidence further indicates that cytokine profiling may serve as an early indicator of disease onset and progression.[21]

The levels of APs (CRP, SAA) and OS markers (MDA) were significantly elevated in patients, while antioxidant defense (TAC) was markedly lower. These results are consistent with the studies which confirm that a systemic inflammation causes acute-phase proteins synthesis and superoxide dismutase inhibition, facilitating the oxidant destruction.[22,23] It should be noted that the results of some investigations have shown less significant alterations than those from the present study, however, these differences have presumably been a result of variations in the severity of disease, comorbidities, or laboratory technique.[24] The present study demonstrates the concurrent elevation of pro-inflammatory and oxidative markers within the same cohort, supporting their complementary role in disease pathogenesis. Even though other studies on tuberculosis biomarkers have made similar findings in prior studies, our results further support the existing knowledge with regard to the interpretation of such pathways and their interactions with each other.[25,26]

These patients also showed hematologic changes such as an increase in WBC count, reduction in hemoglobin, and an increase in platelet count. The high WBCs signify persistent inflammation whereas low hemoglobin is a sign of chronic disease anemia caused by the action of inflammation on iron sequestration. An increase in platelet counts indicates a hypercoagulable and inflammatory condition, as reported earlier,[27,28] but the outcomes of other studies have been inconsistent,[29,30] on individual hematologic parameters since they are simple to measure and indicate inflammation or anemia.

In lipid metabolism, patients had a high level of triglycerides and a low level of HDL-C as compared with the controls, but the LDL-c level was similar. Such findings are consistent with earlier reports by Quinonez et al. that chronic systemic inflammation facilitates dysregulated lipid metabolism, atherogenic profiles, and elevated risk of adverse cardiovascular outcomes.[31,32] The absence of apparent lipid changes imply a selective programming of lipids, which further complicates our perception of lipid regulation in an inflammatory phenomenon.[33] These findings support the view of lipid changes in disease-specific relations, beyond the non-specific changes in lipid fractions.

The observed negative correlation between the inflammatory mediators and the antioxidant potential explains the lopsidedness between the pathogenesis and protective pathways within patients. This concurs with the TB patient interactions identified by Plumlee et al, and implies that multiplex biomarker measure can prove helpful in the analysis of disease severity and response to treatment.[34,35]

Although our work is descriptive, the trends that we found in the increase of inflammatory cytokines, signs of oxidative stress, and lipid alterations give an idea of possible associations in pulmonary tuberculosis. Oxidative stress might be perpetuated through chronic inflammation and then impact lipid metabolism and undermine antioxidant capabilities of the body in a loop that may further promote tissue damage. Reflecting upon these links may assist in practice by indicating patients who may respond to inflammatory-reducing or oxidative stress-reducing treatments, as well as, facilitating more individual responses of disease progression and response to treatment.[36]

We find similar results with international reports of other areas with high incidence of TB (such as Africa and South Asia), where the rise in pro-inflammatory cytokines, the increase of CRP, and the maladaptive lipid metabolism (reduced HDL-C, higher triglycerides) have also been reported.[37] BMI changes, however, differ across regions, presumably due to nutritional, comorbidity, or socioeconomic factors. The above comparisons imply that, although there is extensive overlap between the biological signatures of inflammation, oxidative stress and changes in lipids, there are regional influences that further determine the clinical phenotype of TB patients.[38]

This paper presents an overall assessment of changes in the lipid profiles, demographic variables, inflammatory and oxidative stress variables, hematological measures, and behavioral variables in the patients versus the healthy controls. In contrast to most of the past studies where attention was paid to one type of biomarkers, our study brings out the novelty of an integrated measure of various types of biomarkers in the same cohort. This integrative methodology provides novel information regarding the interaction of inflammation, oxidative stress as well as metabolic dysfunction in pulmonary tuberculosis.

Overall, the clinical, immunological, biochemical, and hematological values of our patients are a complex and combined set of data. The simultaneous evaluation of cytokines, acute-phase proteins, oxidative stress markers, lipid changes, and hematological changes allow our study to find patterns that can be hidden when studied separately. This concomitant assessment highlights the need to factor in a number of biological pathways that would improve the comprehension of TB pathogenesis.

Noteworthy, there are also possible clinical implications of these findings. The set of biomarker phenotype seen here can be used to supplement already existing diagnostic measures like GeneXpert or culture and may be used to assess disease severity, to determine treatment response, or as a predictor of risk of relapse. The quantification of the chosen significant blood markers, including CRP, IL-6, or TAC, may be used as a resource-efficient and inexpensive addition to the current diagnostic and monitoring practices in real-life and especially in resource-depleted environments. These observations require further research including validation with previous studies of composite biomarkers to perfect the results and determine how well it may be applied in clinical practice.

Limitations

The latter research has a number of limitations that should be considered. The nature of cross-sectional design does not allow the investigation of the causal relationships between the changes in the biomarkers and the development of pulmonary tuberculosis, which is why the longevity studies are required to prove all these links in the future. The levels of

the biomarkers were also determined at one point and this prevents the determination of their prognostic applicability or the changes in levels in the process of treatment, relapse or continued disease progression. The results might have been affected by residual confounding factors such as nutritional status, socioeconomic conditions and comorbidities like diabetes or HIV despite the major demographic variables. The research was held at one center in Iraq, which can limit the applicability of the study to more heterogeneous populations and put at risk of selection bias inherent in hospital-based recruitment. Moreover, ELISA assays might have affected the accuracy of biomarker measurement due to variability of measurements. The combination of inflammatory cytokines, acute-phase protein biomarkers, oxidative-stress biomarkers, and hematology indices, however, provides useful information on the immune and metabolic pathophysiology of pulmonary tuberculosis and provides a basis of longitudinal and multicentric studies in the future.

Conclusion

Pulmonary tuberculosis is linked to high amounts of pro-inflammatory cytokines, acute-phase proteins, oxidative stress indicators and typical changes in lipid and haematological phenotypes. These interconnected alterations are the result of a complex interaction of inflammation, oxidative stress, and metabolic disregulation that is part of the disease. Although these observations contribute to the knowledge about the pathophysiological processes, the diagnostic and prognostic value of these biomarkers should be confirmed by larger, heterogeneous cohorts. Future longitudinal studies have been justified to clarify the biomarker dynamics during treatment, disease progression, and response to the therapy and inform the establishment of more customized management interventions to pulmonary tuberculosis.

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Ethical Approval

The study was approved by the Ethics Committee of Al-Habboubi Teaching Hospital in cooperation with the Thi-Qar Health Directorate (approval no. 488). They were well-informed about the objectives and methodologies of the study, and given a written informed consent, and assured that their personal information will be stored under the highest level of confidentiality.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this research.

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AI Use Disclosure

Some of the small sentences and words in the manuscript were checked or language-purified using AI-assisted writing tools with an aim of making it more understandable and to read it better. The researchers fully prepared and wrote all scientific contents, data analysis, and interpretations.

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