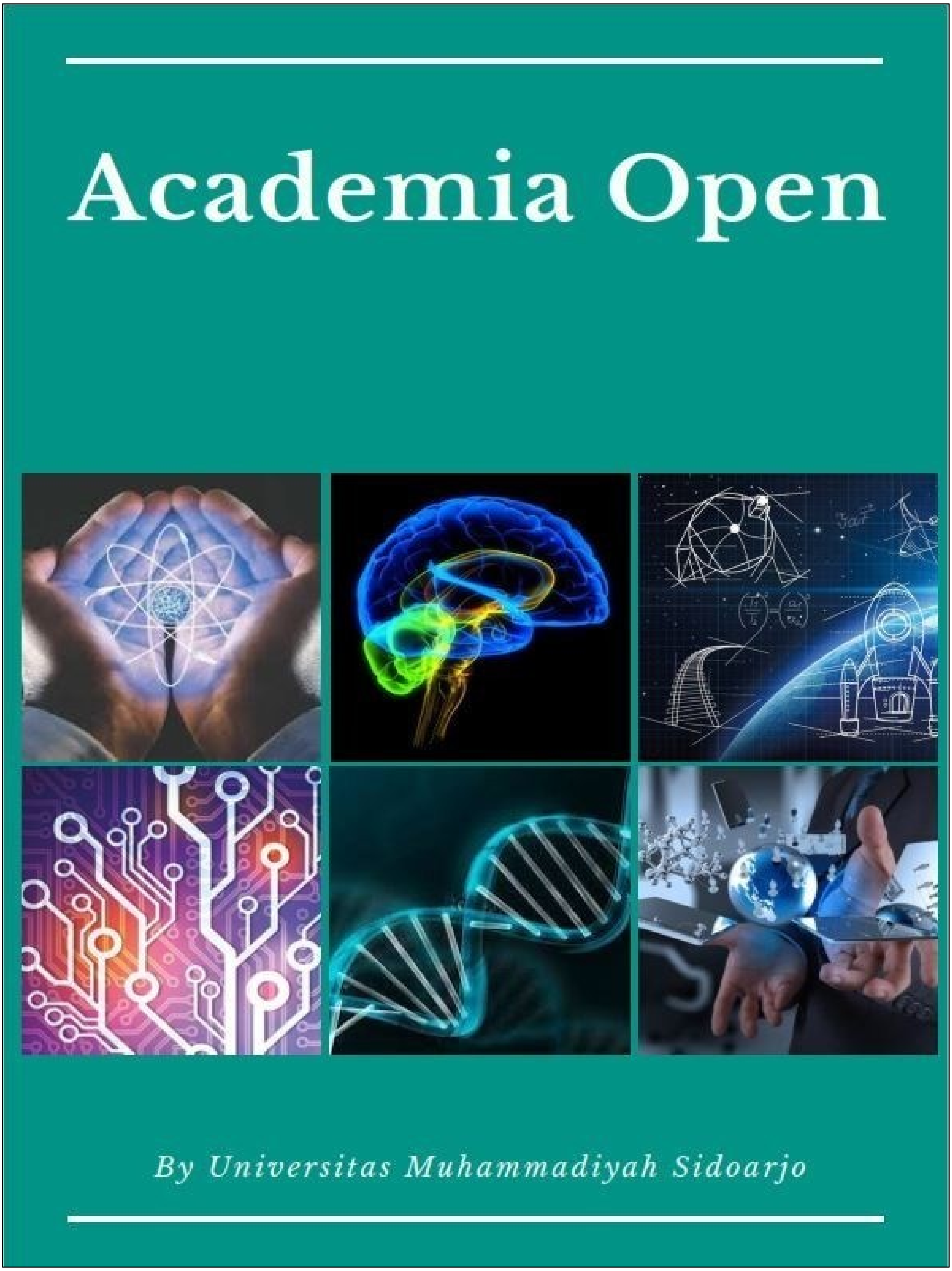
Academia Open

Vol. 10 No. 2 (2025): December

DOI: 10.21070/acopen.10.2025.12854



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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12854

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Academia Open

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DOI: 10.21070/acopen.10.2025.12854

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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12854

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Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12854

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Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12854

Fungal Infections and Their Impact on Cytokine Dysregulation: Biomarkers of Inflammation in Histoplasma capsulatum Infections

Sadam Hameed Rasheed, osamaakram889@gmail.com, (2)
General Directorate for Education of Diyala, Diyala, Iraq

Haneen Kadhim Zaid, osamaakram889@gmail.com (3)
College of Dentistry ,University of Thi-qar

Mustafa Kareem Hassan, osamaakram889@gmail.com (4)
Pathological Analysis Department, Faculty of Applied Medical Science, Al-Shatrah University, Iraq

Osama A. Mohsein, osamaakram889@gmail.com (1)
Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, Thi-Qar, Iraq

(1) Corresponding author

Abstract

General Background: Fungal infections remain a global health concern, particularly in immunocompromised individuals, due to their high morbidity and mortality rates. Specific Background: Among these, Histoplasma capsulatum causes histoplasmosis, a systemic mycosis marked by immune dysregulation and oxidative stress, yet the precise mechanisms linking cytokine imbalance and disease severity remain insufficiently understood. Knowledge Gap: Limited data exist on the concurrent assessment of pro- and anti-inflammatory cytokines and oxidative stress biomarkers in histoplasmosis, especially in non-endemic regions. Aims: This study aimed to evaluate cytokine and oxidative stress profiles in patients with H. capsulatum infection and determine their association with disease severity. Results: Compared to controls, patients exhibited elevated TNF-α, IL-6, IFN-γ, IL-10, TGF-β, CRP, and MDA levels, alongside reduced total antioxidant capacity (TAC), with biomarker levels increasing proportionally with disease severity ($P < 0.001$). Novelty: This is the first study to integrate immunological and oxidative biomarkers in H. capsulatum infection, revealing their interdependent role in pathogenesis. Implications: Findings highlight that simultaneous cytokine and oxidative stress dysregulation underpins disease progression, suggesting that biomarker monitoring could improve prognostic evaluation and guide targeted immunomodulatory therapies.

Highlight :

- The study evaluates cytokine and oxidative stress biomarkers in histoplasmosis patients.
- Results show increased inflammatory markers correlated with disease severity.
- Biomarker monitoring may guide prognosis and improve therapeutic strategies.

Keywords : Histoplasma capsulatum, cytokines, TNF-α, IL-6, IL-10

Published date: 2025-10-24

Introduction

Fungal diseases represent a substantial global public health challenge affecting especially immunocompromised patients and are associated with high mortality and morbidity. In regard to other pathogenic fungi, Histoplasma capsulatum is a dimorphic fungus that causes histoplasmosis, a systemic mycosis of varying clinical presentations ranging from asymptomatic infection to life-threatening disseminated disease 1. Histoplasmosis is the leading endemic mycosis in the USA (Ohio and Mississippi river valleys), people living with HIV/AIDS or vulnerable to TB epidemic are at high risk, and cause of significant outbreaks among cluster of immune-compromised individuals in endemic areas of parts of South (S) America, Central Africa, and Asia and an emerging public health issue3. This pathogen is an obligate biotroph that is inhaled into human lungs in the form of spores, where it undergoes in vivo conversion to a yeast form and then resides predominantly intracellularly (within macrophages), evading immune responses. Accordingly, this intracellular existence leads to intricate hostpathogen interactions which are the pivot of disease cause [5].

The immune response to H. capsulatum has been described as a "high-wire act," balancing the inflammation necessary for immune containment with mechanisms of immune regulation that have evolved to suppress ongoing inflammation and prevent tissue damage. Cytokines are signaling molecules serving as master regulators of this immune response. They should produce pro-inflammatory cytokines (such as TNF-α, IL-6 and IFN-γ) to induce macrophage activation for fungal elimination and the development of an adaptive response [6]. For example, it is well known that TNF-α participates in the formation and maintenance of the granuloma that spreads fungal proliferations and, likewise, IFN-γ induces both microbicidal activity and antigen-presenting function by macrophages [7]. 'The same is true also in a hyper-inflammation scenario where systemic and mucosal homeostasis is preserved by anti-Inflammatory mediators IL-10 and TGF-β; however, over expression of these mediators enable pathogen survive [8]. An abundance of these cytokines (or too little) causes either wide-spread disease, massive disease, or immunopathology. The pathogensis of histoplasmosis is also relevant to oxidative stress A characteristic of the host response to kill intracellular pathogens is the generation of reactive oxygen species (ROS). Nevertheless, increased level of ROS production leads to loss of tissue integrity in the form of oxidative injury like lipid peroxidation, DNA and protein damage which further aggravate the tissue damage [9][10]. When MDA the biomarker malondialdehyde (MDA) to measure, it through the oxidative stress, the total ability of whole organism to scavenge oxidative injuries total Antioxidant Capacity TAC could determine . Assessment of such immunological markers may be helpful for better understanding the inflammatory and oxidative status of the patient which could affect disease severity and prognosis [11].

Substantial changes in profiles of cytokines and biomarkers of inflammation have been reported for patients with systemic fungal infections [12]. As an example, patients with histoplasmosis have increased levels of TNF-α, IL-6 and IFN-g displaying a strong relationship with severity and dissemination of the disease [13]. Furthermore, elevated levels of both IL-10 and TGF-β indicate the activation of regulatory pathways that may inhibit excessive inflammation but may also limit effective fungal clearance [14]. C-reactive protein (CRP) is an acute-phase protein that is typically elevated during systemic fungal infections and is a clinically relevant biomarker of inflammatory burden. However, more detailed studies addressing both pro-and anti-inflammatory cytokines together with oxidative stress biomarkers in histoplasmosis are scarce, particularly outside an endemic area [15].

It's essential to clarify the relationship between hyper dysregulation of cytokines and oxidative stress as potential diagnostic and prognostic biomarkers, and therapeutic strategies. The measurement of inflammatory and regulatory mediators will define immune deficiency mechanisms and will correlate with the extent of disease in patients with histoplasmosis. Furthermore, such studies could have potential clinical implications in the clinical management setting, especially with respect to risk stratification, evaluation of response to treatment and real-time prediction of patients at risk for worse outcome [16].

We designed this study to evaluate the role of Histoplasma capsulatum infection on the cytokines and inflammatory biomarkers including TNF-α, IL-6, IFN-γ, IL-10, TGF-β, CRP, MDA and TAC. The present study was designed to determine differences in these markers between infected individuals and healthy individuals, as well as in correlation with disease severity, shedding light on potential immune and oxidative dysregulations in histoplasmosis.

Methodology

The methods of this research involved being a cross-sectional observational study on cytokine dysregulation and inflammatory biomarkers in patients infected with Histoplasma capsulatum during the period from February 10, 2025 to July 10,2025 at Al-Habboubi Teaching Hospital - Nasiriyah /Iraq. One hundred patients with clinical and laboratory-confirmed histoplasmosis and 50 age/gender-matched healthy controls were included. Patient inclusion criteria were age ≥ 18 years, the presence of a proven histoplasmosis infection, and acceptance to give informed consent Patients with other concomitant infections, auto-immune diseases, cancer, chronic inflammatory condition(s), documented pregnancy or lactation status and those receiving corticosteroids treatment or immunosupressive therapy were not included in this study. The healthy control individuals were chosen based on human health screening realizing from the absence of chronic disease, infection or any mind altering drug. Venous blood (5 mL) was drawn from each patient in sterile vacutainer tubes, 3 mL of which was put into EDTA tubes for separation of plasma and the remaining 2 mL into plain tubes for serum. Samples were processed within 2 hours of collection, after centrifugation at 3000 rpm for 10 min to obtain serum and plasma, supernatants were aliquoted and stored at −80°C until analysis. Serum pro- (TNF-α, IL-6, IFN-γ) and anti-inflammatory cytokine (IL-10, TGF-β) levels and C-reactive protein (CRP) concentration were determined using commercially available ELISA kits following the manufacturer's instructions; oxidative stress markers such as malondialdehyde (MDA), total antioxidant capacity (TAC) by usual spectro-and ELISA photometric methods. All assays implemented duplicates and quaity control samples in each run, OD values were measured by a microplate

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DOI: 10.21070/acopen.10.2025.12854

reader, and the concentrations of C5aRnCA IX-ang and ANGcaptor calculated with calibrators. The Institutional Ethical Committee of Al-Habboubi Teaching Hospital approved the study and written informed consent was obtained from all participants after full explanation of the aims, procedures and possible benefits or drawbacks to be derived from participation in study along with his right to withdraw at any time.

Statistical analysis:

Quantitative data were analyzed using SPSS software version 26. Continuous variables are expressed as mean ± standard deviation (SD), while categorical variables are presented as frequencies and percentages. For variables with a normal distribution, independent and paired two-tailed t-tests were applied to compare differences between groups. Non-normally distributed variables were analyzed using the Mann-Whitney U test or Wilcoxon signed-rank test, as appropriate. Associations between categorical variables were assessed using the Chi-square test. A p-value less than 0.05 was considered statistically significant throughout the analyses.

Ethical approval:

The study was approved by the Human Ethics Committee of Al-Habboubi Teaching Hospital. All participants were fully informed about the study objectives, procedures, and potential risks, and written informed consent was obtained from each participant prior to enrollment. Confidentiality of all personal and clinical information was strictly maintained throughout the study.

Result

Sociodemographic Characteristics of Study Participants

Results of the study indicated that neither age nor gender distribution differed significantly between the patients and the control group: mean age of patients was (42.6 ± 12.3) years versus (41.8 ± 11.7) years among healthy individuals (P = 0.72). Males comprised (58%) of the patients versus (56%) of the controls, P = 0.84 and females comprised (42%) of the patients versus (44%) of the controls, P = 0.81. Such findings suggest that, apart from immune and inflammatory variables, the nature of sociodemographic characteristics of the two groups is comparable thereby strengthening the basis of aiming comparison between them for the rest of the immune and inflammatory variables.Table(1)

Table 1: Comparison Between Patients with *Histoplasma* capsulatum Infections and Healthy Controls

Variable	Patients (n=100)	Controls (n=50)	P-value
Age (years, Mean ± SD)	42.6 ± 12.3	41.8 ± 11.7	0.72
Male (%)	58 (58%)	28 (56%)	0.84
Female (%)	42 (42%)	22 (44%)	0.81

Serum Cytokine Levels in Patients and Controls

In the study, revealing a higher level of inflammatory cytokines in patients infected with Histoplasma capsulatum than in the control group, as the levels of TNF-α were significantly higher, with average (72.4 ± 15.2 pg/mL) compared to (12.6 ± 4.3 pg/mL) in the healthy controls (P<0.001). There was also a higher level of IL-6 in the patients compared with the control group level of (88.5 ± 20.1 pg/mL versus 9.8 ± 3.7 pg/mL, (P<0.001)). Similarly, the levels of IFN-γ increased significantly in the patients (56.2 ± 12.4 pg/mL) compared with (14.5 ± 5.2 pg/mL) in healthy controls (P<0.001). The above outcomes display the immune system is skewed with an influx of inflammatory cytokines appearing in patients, that are part of the pathological immune response to fungal infection.Table(2)

Table 2: Comparison of Inflammatory Biomarkers Between *Histoplasma capsulatum* Infected Patients and Healthy Subjects

Marker	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
TNF-α (pg/mL)	72.4 ± 15.2	12.6 ± 4.3	<0.001
IL-6 (pg/mL)	88.5 ± 20.1	9.8 ± 3.7	<0.001
IFN-γ (pg/mL)	56.2 ± 12.4	14.5 ± 5.2	<0.001

Anti-Inflammatory Cytokine Levels in Patients and Controls

The levels of anti-inflammatory cytokines such as IL-4 (interleukin-4) were significantly increased in patients infected with Histoplasma capsulatum when compared to healthy controls. While the mean IL-10 concentration in the study group was (22.8 ± 6.5 pg/mL), the control group it was (8.2 ± 3.1 pg/mL) (P<0.001). Similarly, TGF-β levels were markedly elevated in patients, at a mean of (18.4 ± 5.7 pg/mL) versus a mean of (7.4 ±2.8 pg/mL) in healthy controls (P<0.001). These findings suggest that an immune response with inhibitory characteristics occurs together with the infection, probably to mitigate the damaging inflammatory response that occurs, albeit at the risk of diminishing effective immune surveillance of the progression of the fungal infection.Table(3)

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Academia Open

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DOI: 10.21070/acopen.10.2025.12854

Table 3: Serum Concentrations of IL-10 and TGF-β in Histoplasma capsulatum Infected Patients Compared to Healthy Controls

Marker	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
IL-10 (pg/mL)	22.8 ± 6.5	8.2 ± 3.1	<0.001
TGF-β (pg/mL)	18.4 ± 5.7	7.4 ± 2.8	<0.001

Inflammatory and Oxidative Stress Biomarkers in Patients and Controls

The results showed significant differences between patients infected with *Histoplasma capsulatum* and the control group with regard to indicators of inflammation and oxidative stress. CRP levels were significantly elevated in patients, with an average of (48.6 ± 14.7 mg/L) compared to (3.2 ± 1.1 mg/L) in healthy controls (P<0.001). MDA concentrations also showed a significant increase in the patient group (6.8 ± 1.5 nmol/mL) compared to (2.1 ± 0.7 nmol/mL) in the control group (P<0.001), reflecting an increase in lipid peroxidation processes. In contrast, TAC values were significantly decreased in patients (0.85 ± 0.22 U/mL) compared to (1.62 ± 0.34 U/mL) in healthy controls (P<0.001), indicating a weakened antioxidant capacity. These results confirm the presence of a distinct inflammatory and oxidative state in patients that contributes to the progression and complications of the disease.Table(4)

Table 4: Comparison of Serum CRP, MDA, and TAC Levels Between *Histoplasma capsulatum* Infected Patients and Healthy Subjects

Marker	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
CRP (mg/L)	48.6 ± 14.7	3.2 ± 1.1	<0.001
MDA (nmol/mL)	6.8 ± 1.5	2.1 ± 0.7	<0.001
TAC (U/mL)	0.85 ± 0.22	1.62 ± 0.34	<0.001

Serum Biomarker Levels According to Disease Severity in Patients with *Histoplasma capsulatum* Infection

Measurement of serum immune and inflammatory markers demonstrated a clear and significant relationship with severity of Histoplasma capsulatum infection. The elevation of TNF-α in the cases was graded from mild 52.3 ± 11.5 pg/mL to moderate 71.6 ± 13.2 pg/mL and severe 89.8 ± 16.4 pg/mL, respectively (P<0.001). For example, IL-6 levels were markedly higher graded by increasing disease severity (mild: 65.2 ± 14.1 pg/mL vs severe: 109.4 ± 18.6 pg/mL; P < 0.001). IL-10, an anti-inflammatory cytokine, was also increased (mild 15.2 ± 4.8 pg/mL to severe 28.6 ± 6.3 pg/mL, P<0.001). Levels of C-reactive peptide in the sera from patients also correlated positively with disease severity, with mean patient level CRP of 32.4±10.2 mg/L in mild disease and 62.5±14.8 mg/L in severe disease (P<0.001) rising steadily by severity category (P<0.001). The accompanying hyper-inflammatory immune response in nearly each spectrum of disease, as either a ratiometric process or a point-in-time profile of inflammatory mediators and cytokines, suggests that at the onset of infection, pathogen loads and a spectrum of host genetic factors dictate the potential range of inflammatory responses.Table(5)

Table 5: Comparison of TNF-α, IL-6, IL-10, and CRP Levels Among Mild, Moderate, and Severe Cases

Marker	**Mild Cases (n=40)**	**Moderate Cases (n=35)**	**Severe Cases (n=25)**	**P-value**
TNF-α (pg/mL)	52.3 ± 11.5	71.6 ± 13.2	89.8 ± 16.4	<0.001
IL-6 (pg/mL)	65.2 ± 14.1	85.7 ± 17.3	109.4 ± 18.6	<0.001
IL-10 (pg/mL)	15.2 ± 4.8	22.1 ± 5.9	28.6 ± 6.3	<0.001
CRP (mg/L)	32.4 ± 10.2	47.8 ± 13.1	62.5 ± 14.8	<0.001

Discussion

To our knowledge, there are no investigations aimed at looking the parallel profile of immunological and inflammatory markers in Histoplasma capsulatum infected patients, meanwhile, we clearly demonstrate that pro-inflammatory/anti-inflammatory cytokines and oxidative stress markers were imbalance. 2.3 Clinical data The age and sex between patients and controls were similar (in years old: 42،6 ± 12 vs 41،8 ±11،7,p>0،05, male-to-female ratio in Table 1) indicating a successful matching o f the two groups! This similarity in standardisation lowers the risk of confounding and increases validity, when comparing immune-inflammation drivers at a later stage 17.

With respect to pro-inflammatory cytokines, TNF-α, IL-6 and IFN-γ levels of patients were higher than those of controls. TNF-α value was mean=72.4±15.2 and the that of IL-6 was mean;88.5±20.1 pg / ml(P.. 001) whereas, IFN-γ average valu e =56.2±05 ppg/ml comparing to control cytok ine's a verage val ueof14Expecting cut off values of TNF-αlPG (95% CI),5IL-

Academia Open
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DOI: 10.21070/acopen.10.2025.12854

61pg/lml(90%),16IFNγ46pg/lml()86!%). 5±5.2 pg/ml(P<0.001). These findings mirror current reports on other fungal infection model systems (including histoplasmosis) of plastic Th1 type response, defined by exaggerated secretion/signals of pathogenic pro-inflammatory cytokines obligatory to pathogen destruction and the collateral target tissue damage induced 19. In fact, no difference in the secretion of TNF-α and IFN-γ was observed between animals with acute or chronic infection, supporting these data [21]. Nonetheless, low IFN-γ levels of mild cases as Valdez et Al., were observed in some other researches that might be caused by tested phase of the disease or load on infectious agent and genetic variation from host [22].

We also observe a raise in anti-inflammatory factors of (IL 10 and TGF β:22.8±6.5pg/mL,18.4±5.7pg/mL) levels in patients compared to controls (8.2±3.1pg/mL,7.4+2/8 pg/ml)(P<0,001) [23], [24]. This enhancement indicates the induction of regulatory processes which prevent a harmful excessive inflammatory reaction. The concomitant upregulation of pro-inflammatory and anti-inflammatory cytokines, hence, demonstrates a counterregulatory immune response which corresponds to the damped wave-like immunoregulation as observed in systemic mycoses 23 [25], [26]. However, some studies observed a slight elevation of IL-10 production during T:V infection that may be due to differences in the occurrence of cytokine measurement as the expression level is regulated constantly but peaks at different time points post-infection 25. Measurement showing of oxidative stress revealed that patients had significantly higher CRP and MDA (48.6±14.7 mg/L and 6.8 ±1,5 nmol/mL) when compared with controls (3.2 ± 1.lmg/Land 2.I±0(l:tnmol/mL),whileTAC was significantly lower(0,85-t-022U/mlvs Ii62§(-54)iml,P

When stratified with the disease severity, we observed a gradual increase in TNF-α, IL-6, IL-10 and CRP levels from mild to severe patients detected, demonstrating that cytokine imbalance was positively associated with clinical severity. In particular, the level of TNF-α were elevated from 52.3 ± 11.5 pg/mL in mild cases to 71.6 ± 13.2 pg/mL in moderate cases and up to 89.8 ± l6.4 pg/mL.(P <0.001). The corresponding values of IL-6 were 65.2 ± 14.1 pg/mL, 85.7 ± 17.3 pg/mL and 109.4 ± 18.6 pg/mL (P <0·001). The levels of IL-10 were significantly increased from 15.2 ± 4.8 pg/mL in mild cases to 22.1 ±5.9 pg/mL in moderate cases and 28.6 ±6.3 inspired by the finding that the picture was different between type of patient (P <0.001). CRP levels exhibited a similar trend, ranging from 32.4 ± 10.2 mg/L in mild (21-29 points) to 47.8 ± 13.1 mg/L moderate (14-20 points) and then to severe ranges of illness, with levels increasing at severe clinical stage to 62.5 ± 14.8 mg/L (P < 0.001). Our results are consistent with these studies, which had also linked TNF-α and IL-6 dysregulation to more severe histoplasmosis disease course [30]. Co-elevation of IL-10 may indicate the involvement of antiviral feed-back loops in attempted short circuiting harmful inflammatory responses and limiting tissue damage throughout disease progression [31].

Conclusion

Simultaneous elevation of pro- and anti-inflammatory cytokines and oxidative stress markers suggests tug-of-war between immune stimulant and immunosuppressant in mycosis. The inconsistency in outcomes for the five studies could be due to variant disease length, pathogen virulence, host immune status and methods used for biosignature determination. In total, these findings indicate that the investigation of inflammatory and regulatory pathways, as oxidative stress with them, provide a more complete view of disease progression as well as potential novel targets for therapeutic intervention in treatment of H. capsulatum infections. The simultaneous induction of pro- and anti-inflammatory cytokines, as well as oxidative stress markers representative of an immune stimulatory response and an immunosuppressive one is evidencing a hypothetical equilibrium between immune stimuli and immune depression in mycosis. This concomitant rise also highlights the intricate nature of the immune response during fungal infection, with particular reference to H. capsulatum infection where subversion of host immune responses has been enshrined as a hallmark of disease establishment. The inconsistencies of these studies may in part be accounted for by the variations in course of disease, pathogen virulence, host immune status and detection assays for biomarkers. These differences highlight the need for standardized approaches to biomarker assessment that will enable interpretation across studies. Monitoring some of these pathways as the inflammatory and regulatory ones are engaged in these infections, including its oxidative status may permit to further understand the pathogenesis of this condition. Further, better understanding of the balance of immune activation versus suppression could lead to identification of new targets for therapy which can translate to improved management of H. capsulatum infections. Taken together these data support the need for a global perception of immune reactivity in mycosis rather than a dichotomous classification and indicate an avenue for intervention through targeted therapy on pathophysiological pathways ultrastructural morphology that bridge both inflammatory and immunoregulatory responses.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

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