

The Role of Soluble Tumor Necrosis Factor Receptor II as a Prognostic Marker in Severe COVID-19

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ABSTRACT

Objective: To investigate the clinical disease characteristics and standard laboratory parameters in relation to specific cytokine biomarkers associated with COVID-19 sequelae and to elucidate their correlations with disease severity, respiratory support requirements, and patient outcomes

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Diyala, Iraq, from 1st December 2024 to 30th April 2025.

Methods: Seventy four participants were enrolled and divided in two groups, patient group and control group. Patient group comprised 44 participants and control group consisting of thirty participants.

The Iraqi Ministry of Health devised the COVID-19 severity protocol, and those steps were used to grade the patients.

Results: There was a significant indicators of disease due to their relationship with COVID-19 and a high correlation between the severity of COVID-19 and inflammatory markers, including TNFR2, while blood cells, neutrophils and lymphocytes. There was a substantial rise in tumor necrosis factor receptor II levels ($P < 0.001$) between the control and sick groups.

Conclusion: The levels of tumor necrosis factor receptor II, white blood cells, neutrophils, and lymphocytes, all of which were consistent with the infection, were correlated with the severity of the COVID-19 infection.

Key Words: COVID-19, Tumor necrosis factor receptor II (TNFR2), White blood cells (WBCs), Neutrophil, Lymphocytes.

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INTRODUCTION

The COVID-19 pandemic has created a challenging environment for research, society, and the medical community. The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has an unpredictable clinical course that might worsen the illness and have fatal consequences. For patients to get medicine on time, effective molecular biomarkers that can classify them based on risk must be developed¹⁻³.

The COVID-19 pandemic has led to increased morbidity, placing strain on hospital infrastructure and

resources. Developing trustworthy measures of disease severity and death is crucial for distributing healthcare funds and improving treatment results⁴.

The role of many biomarkers in predicting COVID-19 patient prognosis is now under investigation. TNFR2 is one such biomarker of interest, along with lymphocytes, neutrophils, and WBCs. This is particularly significant since in the past, people with other viral infections who had higher concentrations of the chemical experienced poorer results. The pleiotropic cytokine tumor necrosis factor (TNF) is thought to be crucial for coordinating a range of immune responses, the onset of illness, and the survival and division of cells. TNF limits the inflammatory reaction's spread after the invasion is mitigated or stopped by triggering a quick and strong immune response in the host's defense against infections⁵. Pro-inflammatory cytokines including IL-6, IL-8, chemokines, and even the substance itself are stimulated by it⁶. TNF- α promotes inflammation by attracting immune cells to the site of inflammation, such as neutrophils, monocytes, and lymphocytes⁷. Under some circumstances, Tumor necrosis factor is capable of inducing both apoptotic and necrotic cell death pathways⁸. Interestingly, macrophages and monocytes are among the main producers of Sensitivity

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to TNF is cell-type dependent. While some cells display a strong sensitivity, others, including T cell subsets, natural killer cells, dendritic cells, B cells, and astrocytes, are producers of TNF, but at lower concentrations⁹. Tumor necrosis factor is a stable form of 233 amino acid homotrimers and a type II transmembrane protein¹⁰. Multiple sources substantiate TNF's anti-inflammatory effect in the chronic phase of numerous inflammatory illnesses and infections, in addition to its prominent pro-inflammatory activity¹¹. Leukocytes, another name for WBCs are immune system cells that help defend the human body employs leukocytes as a defense mechanism against exogenous pathogens and infectious agents. Hematopoietic stem cells, residing within the bone marrow and characterized by their multipotency, serve as the origin for all leukocyte lineages. These leukocytes are distributed throughout the organism, including within the circulatory and lymphatic systems¹². White blood cell count is a significant component of total blood count because leukocyte count is frequently used as a sign of illness. In microliters of blood, a typical white cell count is often stated as 4,000–11,000 WBC.

It was discovered that, in comparison to patients with less severe illness, Patients presenting with severe or critical COVID-19 exhibited elevated markers indicative of innate immune system activation. Significantly reduced amounts of lymphocytes and their subtypes was another marker of a compromised adaptive immune response in severe or critical COVID-19 patients¹³.

METHODS

This case control study was conducted at Diyala, Iraq from 1st December 2024 to 30th April 2025 vide letter No. MEC-24044/Approval/JSDJNEHU Dated November 4, 2024. Seventy four participants were enrolled. They were divided in two groups, patient group and control group. In patient group, 44 participants were enrolled. The control group, consisting of thirty participants, displayed a healthy physiological state and was serologically negative blood test findings for antibodies against harmful bacteria, in order to check for COVID-19 IgG/IgM. They also employed the AFIAS-6 New instrument. Nasopharyngeal swabs and genetic testing were used to determine the COVID-19 status of patients. Common complaints were headaches, constipation, runny noses, sore tongues, dyspnea, and decreased appetite. Ten milliliters of venous blood were taken from the patient, and four tubes were used for coagulation, biochemical, hematological, and coagulation testing. The ELISA test sera were split into aliquots and stored. The control group, consisting of thirty participants, displayed a healthy physiological state and was serologically

negative blood test findings for antibodies against harmful bacteria, in order to check for COVID-19 IgG/IgM. They also employed the AFIAS-6 New instrument. The data was entered and analyzed through SPSS-25.

RESULTS

The serum TNFR II concentrations, expressed as mean $\pm$ standard deviation, for both the patient and control groups. The significant difference ($P < 0.05$) indicated by statistical analysis between critical and moderate patient groups, and a highly significant elevation ($P < 0.001$) in the moderate patient group compared to the control group (Table 1, Fig. 1).

Table 2 revealed no statistically significant differences ($P > 0.05$) in TNFR II levels between females and males within either the control or patient groups. However, a highly significant increase ($P < 0.001$) was observed in male patients compared to male controls, and similarly in female patients compared to female controls.

Table 3 presents the serum levels of white blood cells (WBC), neutrophils, and lymphocytes, expressed as mean $\pm$ standard deviation, for both patient and control groups. A highly significant decrease ($P < 0.001$) in lymphocyte levels and a highly significant increase ($P < 0.001$) in WBC and neutrophil levels were observed in the patient group compared to the control group.

Table No. 1: Mean TNFR II concentrations among the study groups

Biomarker	Control (N = 30)	Moderate Patients (N=42)	Critical Patients (N=18)
TNFR II	62.5 $\pm$ 3.2	91.4 $\pm$ 5.0	97.1 $\pm$ 5.7

Controls vs Moderate patients $P < 0.001$

Control vs Critical patients $P < 0.001$

Moderate patients vs critical patients $P < 0.05$

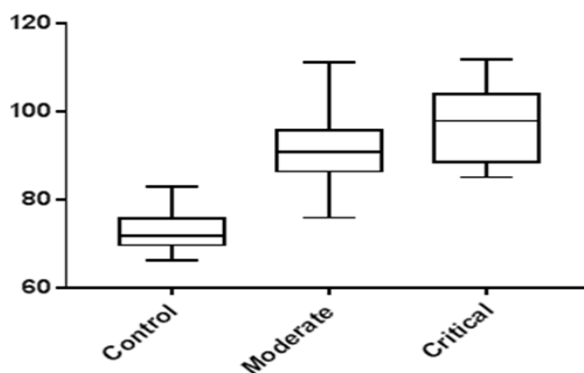


Figure No. 1: TNFR II levels in the control, moderate and critical groups

Table No. 2: Mean TNFR2 levels according to gender and age among controls and patients

Variable	Group	Control (N=30)	Patients (N=44)
Gender	Male	73.0±5.8	88.01±5.90
	Female	73.11±3.9	95.60±9.67
Age (years)	Controls (18–45)	72.07±6.22	85.40±7.52
	Patients (45–75)	73.01±4.88	99.02±8.21

Male control vs male patients $P < 0.001$

Female control vs female patients $P < 0.001$

Table No. 3: Mean leukocyte, neutrophil, and lymphocyte counts were determined for the patient and control groups

Variable	Controls	Patients	P value
White blood cells	6.83±0.23	19.0±0.34	<0.001
Lymphocyte	33.7±4.1	9.6±0.9	<0.001
Neutrophil	60.2±4.72	79.1±6.7	<0.001

DISCUSSION

In the present study, there was no significant ($P > 0.05$) difference in TNFR2 levels between age group in patients and control groups. However, a highly significant elevation ($P < 0.001$) was observed in patients compared to controls. The present results align with the findings of Gohda et al¹⁴ who reported that TNFR levels were significantly elevated in patients with severe disease, but not in those with mild to moderate disease. These differential profiles may elucidate the observed association between elevated TNFR and increased mortality in COVID-19 patients. Specifically, high TNFR2 levels correlated with mortality when relevant clinical parameters were considered. When a serious sickness started, TNFR levels sharply rose. Nonetheless, there was no difference in these biomarker levels between individuals with intermediate II and severe disease. Furthermore, TNFR levels did not change between individuals with mild-to-moderate disease, and the data showed no difference between moderate and critical patients.

Palacios et al¹⁵ shown that elevated ADAM17 expression, not overproduction, is the cause of elevated TNFR levels. Notably, whereas TNFR2 levels were the same in all severity groups, however, no significant difference was observed relative to patients with moderate disease and contrast to their findings, the severity of the illness was correlated with both TNFR levels. These variations might be partly explained by variations in the ELISA kit, variations in the clinical stratification of COVID-19, and variations in ethnicity, among other etiologies.

Prior investigations on COVID-19 have demonstrated that patients presenting with severe symptoms commonly exhibit elevated white blood cell counts upon initial admission¹⁶.

Zhu et al¹⁷ found that in COVID-19, higher total WBC levels were linked to death which, given the observed declines in lymphocyte counts, suggested that elevated neutrophils were the main factor responsible for the rise in WBCs. The inflammatory condition and cytokine storm can account for this activation mechanism¹⁸. Increases in neutrophils have also been linked to lung tissue in addition to the circulation¹⁹. Increased infiltration of immature neutrophils causes an aberrant immunological response in the lungs of individuals with severe illness²⁰.

Neutrophilia, excluding cases complicated by bacterial infection or super-infection, correlates with a hyper-inflammatory state and cytokine storm, both critical components of the COVID-19 pathogenic mechanism. Notably, neutrophils are implicated in the pathogenesis of several viral respiratory illnesses associated with acute respiratory distress syndrome²¹. A subset of individuals exhibits leukocytosis coupled with neutrophilia, which appears to correlate with increased disease severity²². An increase in circulating neutrophil counts correlates with COVID-19 disease progression; consequently, neutrophilia is recognized as a marker of severe respiratory disease and poor clinical outcome²³. Individuals presenting with severe COVID-19 infection exhibited significantly elevated leukocyte and neutrophil counts compared to those with non-severe infections²⁴.

There have been reports of an increase in neutrophils in lung tissue as well as the circulation¹⁹. The pathological immune response observed in the lungs of patients with severe COVID-19 is partially attributable to the increased infiltration of immature and/or dysfunctional neutrophils. Similar to other viral infections, SARS-CoV-2 induces the formation of neutrophil extracellular traps, which may contribute to tissue damage. In COVID-19, dysregulated neutrophil activation can exacerbate the host's inflammatory response²⁵. Neutrophils contribute significantly to the hyper-inflammatory state associated with COVID-19 pathogenesis through enhanced cytokine production and degranulation²⁶. Given the observed correlation between neutrophilia and adverse outcomes, alterations in peripheral blood or tissue neutrophil counts have been proposed as potential exclusive indicators of pulmonary injury in COVID-19 patients^{27,28}. Validation of these data may provide a rationale for targeting neutrophils and their recruitment mediators as a means to attenuate COVID-19 disease severity¹⁸.

It is widely known that various virus types modify the total number of lymphocytes as well as their subsets, suggesting a possible link between changes in the lymphocyte subset and viral pathogenic processes²⁹. A viral attachment may directly induce lymphopenia, or immunological damage from inflammatory mediators may cause it indirectly. Furthermore, lymphopenia may also result from the exudation of circulating

lymphocytes into inflammatory lung tissues. The decrease in lymphocyte subset counts in COVID-19 patients was assessed through a comprehensive analysis of twenty peer-reviewed studies that detailed both lymphocyte subset counts and disease severity¹⁸.

CONCLUSION

Tumor necrosis factor receptor II has therapeutic utility. The correlation was established between the clinical severity of CO-19 and the observed levels of white blood cell counts, neutrophil counts, lymphocyte counts and tumor necrosis factor receptor II.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Muayad AL-Dulaimi, Saleh A.H
Drafting or Revising Critically:	Muayad AL-Dulaimi, Mohammad Mutlag Salih
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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