ORİJİNAL MAKALE / ORIGINAL ARTICLE

Sağlık Bilimlerinde Değer / Sağlık Bil Değer
Value in Health Sciences / Value Health Sci
ISSN: 2792-0542 sabd@duzce.edu.tr 2024; 14(1): 46-53
doi: https://dx.doi.org/10.33631/sabd.1240226

Factors Affecting TNF-α Decrease in COVID-19 Patients

Muhammet GÜLHAN[1], Merve ALPAY[2], Şule YILDIZ[3], Nevra Ezgi YAŞLI[3], Murat ACAT[4], Gözde KAHRAMAN[5], Peri ARBAK[3]

ABSTRACT

Aim: Tumor necrosis factor-alpha (TNF-α) have several functions, including cell survival, differentiation, and proliferation. TNF-α may effect the cell death during the cytokine storm that occurred during COVID-19 infection. We aimed to investigate, the factors that affects the TNF-α decrease in COVID-19 patients.

Material and Methods: Totally 44 individuals with COVID-19 infection were included the study. Blood counts, biochemical examinations and D-dimer examinations were obtained. Comorbidities and initial symptoms of the patients were recorded. TNF-α, CRP and ferritin values were measured twice on the 1st and 7th days of hospitalization. The change in this values were examined according to comorbidities, initial symptoms and steroid usage.

Results: Of a total of 44 patients, 56.8% were male (25/44) and 43.2 % were female (19/44). TNF-α decrease was found to be statistically significant in non-diabetic patients, while TNF-α decrease was found to be insignificant in diabetic patients. CRP decrease was found to be statistically significant in both diabetic and non-diabetic patients while ferritin decrease was insignificant in both diabetic and non-diabetic patients. While TNF-α and CRP decreased statistically significantly in those without lung disease, it was observed that both TNF-α and CRP decreases were not significant in those with lung disease. The decrease in TNF-α and CRP was statistically insignificant in those who did not treated with steroids, while the decrease in TNF-α and CRP was significant in those who treated with steroids.

Conclusion: Steroids decreases the TNF-α levels. TNF decrease is not significant in those with diabetes and lung disease.

Keywords: Tumor necrosis factor-alpha; C-reactive protein; COVID-19; diabetes mellitus.

COVID-19 Hastalarında TNF-α Düşüşünü Etkileyen Faktörler

ÖZ

Amaç: Tümör nekrozis faktör-alfa (TNF-α) hücrenin hayatta kalması, farklılaşması ve çoğalması da dahil çeşitli işlevlere sahiptir. TNF-α, COVID-19 enfeksiyonu sırasında ortaya çıkan sitokin fırtınası sırasında hücre ölümünü etkileyebilir. Bu çalışmada COVID-19 hastalarında TNF-α düşüşüne etki eden faktörleri araştırmak amaçlandı.

Gereç ve Yöntemler: Çalışmaya COVID-19 enfeksiyonu olan toplam 44 kişi dahil edildi. Kan sayımı, biyokimyasal incelemeler ve D-dimer incelemeleri yapıldı. Hastaların ek hastalıkları ve başlangıç semptomları kaydedildi. TNF-α, CRP ve ferritin değerleri yatışının 1. ve 7. günlerinde iki kez ölçüldü. Bu değerlerdeki değişim komorbiditelere, başlangıç semptomlarına ve steroid kullanımına göre incelendi.

Bulgular: Toplam 44 hastanın %56,8'i erkek (25/44) ve %43,2'si kadındı (19/44). TNF-α düşüşü diyabetik olmayan hastalarda istatistiksel olarak anlamlı bulunurken, diyabetik hastalarda TNF-α düşüşü anlamsız bulundu. CRP düşüşü hem diyabetik hem de diyabetik olmayan hastalarda istatistiksel olarak anlamlı bulunurken, ferritin düşüşü hem diyabetik hem de diyabetik olmayan hastalarda anlamsız bulundu. Akciğer hastalığı olmayanlarda TNF-α ve CRP istatistiksel olarak anlamlı düzeyde düşerken, akciğer hastalığı olanlarda hem TNF-α hem de CRP düşüşlerinin anlamlı olmadığı görüldü. TNF-α ve CRP'deki azalma steroid ile tedavi edilmeyenlerde anlamlı değilken, TNF-α ve CRP'deki azalma steroid tedavisi alanlarda istatistiksel olarak anlamlıydı.

Sonuç: Steroidler TNF-α düzeyini düşürürler. Akciğer hastalığı ve diyabeti olanlarda TNF-α düşüşü anlamlı değildir.

Anahtar Kelimeler: Tümör nekrozis faktör-alfa; C-reaktif protein; COVID-19; diyabetes mellitus.

[1] Düzce State Hospital, Department of Infection Diseases, Kastamonu, Turkey.
[2] Duzce University Faculty of Medicine, Department of Medical Biochemistry, Duzce, Turkey.
[3] Duzce University Faculty of Medicine, Department of Pulmonology, Duzce, Turkey.
[4] Karabuk University Training and Research Hospital, Department of Pulmonology, Karabuk, Turkey.
[5] Duzce University Faculty of Medicine, Department of Medical Microbiology, Duzce, Turkey.

Sorumlu Yazar / Corresponding Autho Muhammet Gülhan, e-mail: mustafammg@hotmail.com
Geliş Tarihi / Received: 02.02.2023, Kabul Tarihi / Accepted: 14.11.2023

INTRODUCTION

Although tumor necrosis factor-alpha (TNF-α) was previously considered a factor that induced tumor necrosis, it was later observed to have several functions, including cell survival, differentiation, and proliferation. It was reported that inappropriate or excessive TNF-α activation was also associated with chronic inflammation and could lead to autoimmune diseases (1).

The role of TNF-α in the prognosis of COVID-19 has not yet been clearly understood. Mouse experiments have presented evidence that the TNF-α and interferon-gamma (IFN-γ) combination accounted for cell death during the cytokine storm that occurred during COVID-19 infection. Further, the study demonstrated that the combination activated Janus kinase/signal transducer and activator of transcription 1/interferon regulatory factor 1 (JAK/STAT1/IRF1) and induced nitric oxide production, which resulted in PANoptosis by the activation of the Caspase-8/Fas-associated protein with death domain (FADD)-mediated pathway. It was also shown that anti-TNF-α use and Anti-INF-γ monoclonal antibodies protected mice from mortality (2).

Many studies have suggested that the severity of disease was associated with TNF-α, C-reactive protein (CRP), and ferritin levels in the course of COVID-19 infection (3-5).

The present study investigated the change in TNF-α levels in patients with COVID-19 and whether the foregoing change was associated with comorbidities and patient complaints. Additionally, the effect of methylprednisolone therapy on TNF-α level changes was investigated under the scope of the study.

MATERIAL AND METHODS

Study population

Totally 44 individuals (male=25; female=19) with COVID-19 infection were included in the current study. TNF alpha values of 5 patients could not be detected within the specified value range. Therefore, statistical analysis was performed on 39 patients. We collected the epidemiological and clinical data from medical records. Patients who had positive combined nasopharyngeal-orapharyngeal RT-PCR swab samples. The combined nasopharyngeal-oropharyngeal real-timepolymerase chain reaction (RT-PCR) swab samples, blood counts, biochemical examinations and D-dimer examinations were obtained from these patients.

This study was approved by the Duzce University Medical Faculty ethics committee (dated 15.02.2021 and numbered 42).

Statistical Analysis

Normally distributed values were given as mean and standard deviation (SD). Median and range values were given for values that did not show normal distribution. The Shapiro-Wilk test of normality was applied to assess whether the data tested resulted from a normally distributed population. Parametric T-Test was used for normally distributed and skewed variables, and non-parametric Mann-Whitney test was used for non-normally distributed variables. Paired T-Test was used to compare the mean values of a variable obtained in different periods. The level of significance was taken as 0.05.

Data analysis

Our research was carried out on 44 COVID-19 patients who were hospitalized in the pandemic service of Duzce University Hospital, Kastamonu Training and Research Hospital and Karabuk University Hospital as of August 2020. All applicants were informed about the study and their demographic data were evaluated. The main purpose of our study is to determine the change in the TNF-α values measured in determined time periods depending on the course of the disease in COVID-19 patients and to interpret TNF-α as a prognostic indicator.

Biochemical analysis was performed in blood samples taken after at least 12-14 hours of fasting, provided sterilization conditions, at 4°C and serum samples separated by centrifugation at 3000 rpm for 15 minutes. The routine parameters of the blood samples taken on the 1st and 7th days during hospitalization were determined by the colorimetric method in the IDS analyzer B0728 autoanalyzer device; The remaining sample was kept in suitable storage conditions and measured by spectrophotometric method in Grifols Tritunus Microelisa device (450 nm OD) following the commercially purchased Human TNF-α ELISA kit (Elabscience, TX) protocol. The kit linearity used for TNF-α levels of the evaluated samples was taken as reference between 7.81-500pg/mL, and the sensitivity was between 4.69pg/mL.

RESULTS

Total 44 patients hospitalized in January 2021 were included to study. CRP and ferritin were evaluated on 44 patients. The TNF-α results of 5 patients were non-standard, so the evaluation of TNF-α results done for 39 patients. Of a total of 44 patients, 56.8% were male (25/44) and 43.2 % were female (19/44). The mean age of the patients was 64.7 ± 16.9 (min 27- max 94). 7 patient have lung diseases. (asthma 4, chronic obstructive pulmonary disease 3). Comorbidities and initial symptoms of the patients are shown in Table 1.

Table 1. comorbidities and initial symptoms of patients

Comorbidities	Number (n=39)	%
Diabetes mellitus (+)	11	25.0
Diabetes mellitus (-)	33	75.0
Hypertension (+)	18	40.9
Hypertension (-)	26	59.1
Chronic renal failure (+)	4	9.1
Chronic renal failure (-)	40	90.9
Lung disease (+)	7	15.9
Lung disease (-)	37	84.1
Ischemic heart disease/Heart failure (+)	8	18.2
Ischemic heart disease/Heart failure (-)	36	81.8
Central nervous system disease (+)	5	11.4
Central nervous system disease (-)	39	88.6
Malignancy (+)	4	9.1
Malignancy (-)	40	90.9
Initial Symptoms		
Fever	9	20.5
Dyspnea	28	63.6
Cough	18	40.9
Headache	5	11.4
Throat ache	2	4.5
Weakness	21	47.7
Smell/ taste loss	1	2.3
Myalgia	8	18.2
Nausea-Vomiting	1	2.3

TNF-α values were measured twice on the 1st and 7th days of hospitalization. CRP and ferritin results were also evaluated on the same days. Anti-inflammatory therapy was given to patients who needed it. Of 44 patients, 1 received tocilizumab, 6 received high-dose steroid (250 mg and above) and 19 received low-dose steroid (80 mg and below). 14 patient received both high-dose and low-dose (first low-dose, then continued with high-dose).

Table 2. TNF-α, CRP and Ferritin changes according to comorbidities

	Mean	SS	Median	Minimum	Maximum	p
Diabetes mellitus (+)						
TNF-α (Day 1)	378.7	339.2	313.6	71.4	1266	0.093
TNF-α (Day 7)	297.8	272.6	229.7	57.1	930.1	
CRP (Day 1)	76.6	29.0	63.7	11.0	180	0.008
CRP (Day 7)	29.0	33.0	18.2	5.0	111.2	
Ferritin (Day 1)	349.9	285.8	227.5	114.0	1037.0	0.374
Ferritin (Day 7)	502.0	414.6	489.0	114.0	1360.7	
Diabetes mellitus (-)						
TNF-α (Day 1)	297.1	161.6	321.7	28.5	567.0	<0.001
TNF-α (Day 7)	175.0	126.3	195.5	15.9	440.8	
CRP (Day 1)	92.5	74.3	85.0	2.0	257.0	<0.001
CRP (Day 7)	30.9	42.6	16.0	0.7	203.0	
Ferritin (Day 1)	308.3	258.6	278.0	18.0	1010.0	0.139
Ferritin (Day 7)	394.9	339.5	329.0	15.0	1463.0	
Hypertension (+)						
TNF-α (Day 1)	390.6	269.2	321.7	43.2	1266.0	0.001
TNF-α (Day 7)	229.5	227.0	202.7	22.7	930.1	
CRP (Day 1)	94.8	88.6	79.0	2.0	257.0	<0.001
CRP (Day 7)	19.8	24.8	16.0	2.0	111.2	
Ferritin (Day 1)	282.0	223.3	245.4	23.0	1037.0	0.163
Ferritin (Day 7)	403.0	344.7	374.0	15.0	1360.7	
Hypertension (-)						
TNF-α (Day 1)	267.5	163.3	255.2	28.5	567.0	0.001
TNF-α (Day 7)	182.8	123.4	207.2	15.9	440.8	
CRP (Day 1)	84.1	58.7	81.0	3.0	190.0	0.005
CRP (Day 7)	38.5	47.6	16.0	0.7	203.0	
Ferritin (Day 1)	345.5	289.7	212.0	18.0	1010.0	0.354
Ferritin (Day 7)	433.4	371.7	269.4	57.0	1463.0	
Ischemic heart disease						
TNF-α (Day 1)	283.8	145.4	305.5	71.4	438.3	0.018
TNF-α (Day 7)	184.2	110.8	202.7	26.7	310.8	
CRP (Day 1)	94.3	71.8	77.0	11.0	192.0	0.017
CRP (Day 7)	26.6	34.8	12.0	8.0	111.2	
Ferritin (Day 1)	374.4	319.5	245.4	88.0	1010.0	0.093
Ferritin (Day 7)	626.8	449.2	507.0	67.0	1360.7	
Ischemic heart disease						
TNF-α (Day 1)	325.5	232.8	321.7	28.5	1266.0	<0.001
TNF-α (Day 7)	206.6	186.0	207.2	15.9	930.1	
CRP (Day 1)	87.2	72.6	82.0	2.0	257.0	<0.001
CRP (Day 7)	31.4	41.8	16.0	0.7	203.0	
Ferritin (Day 1)	306.3	252.0	226.5	18.0	1037.0	0.317
Ferritin (Day 7)	371.8	319.7	269.4	15.0	1463.0	
Lung Disease (+)						
TNF-α (Day 1)	220.8	95.8	224.7	116.7	309.0	0.463
TNF-α (Day 7)	177.2	118.8	210.8	26.7	305.0	
CRP (Day 1)	71.1	48.2	72.0	17.0	162.1	0.063
CRP (Day 7)	38.8	36.6	27.0	10.0	115.5	
Ferritin (Day 1)	187.9	111.8	164.1	80.0	412.0	0.237
Ferritin (Day 7)	214.1	137.7	195.2	63.0	448.0	
Lung Disease (-)						
TNF-α (Day 1)	335.7	230.7	369.2	28.5	1266.0	<0.001
TNF-α (Day 7)	207.3	182.9	195.5	15.9	930.1	
CRP (Day 1)	91.8	75.4	89.0	2.0	257.0	<0.001
CRP (Day 7)	28.8	41.2	15.0	0.7	203.0	
Ferritin (Day 1)	344.4	277.0	253.0	18.0	1037.0	0.143
Ferritin (Day 7)	461.7	373.2	382.0	15.0	1463.0	

TNF-α: Tumor necrosis factor-alpha, **CRP:** C-reactive protein

Five patients were not given any anti-inflammatory treatment. It was evaluated whether comorbidities, initial complaints and steroid use affect these biochemical parameters, especially TNF-α.

TNF-α decrease was found to be insignificant in diabetic patients, while TNF-α decrease was found to be significant in non-diabetic patients. CRP decrease was found to be significant in both diabetic and non-diabetic patients while ferritin decrease was insignificant in both diabetic and non-diabetic patients (Table 2, Figure 1a).

While TNF-α and CRP decreased significantly in those without lung disease and ischemic heart disease, it was observed that both TNF-α and CRP decreases were not significant in those with lung disease and ischemic heart disease (Table 2, Figure 1b).

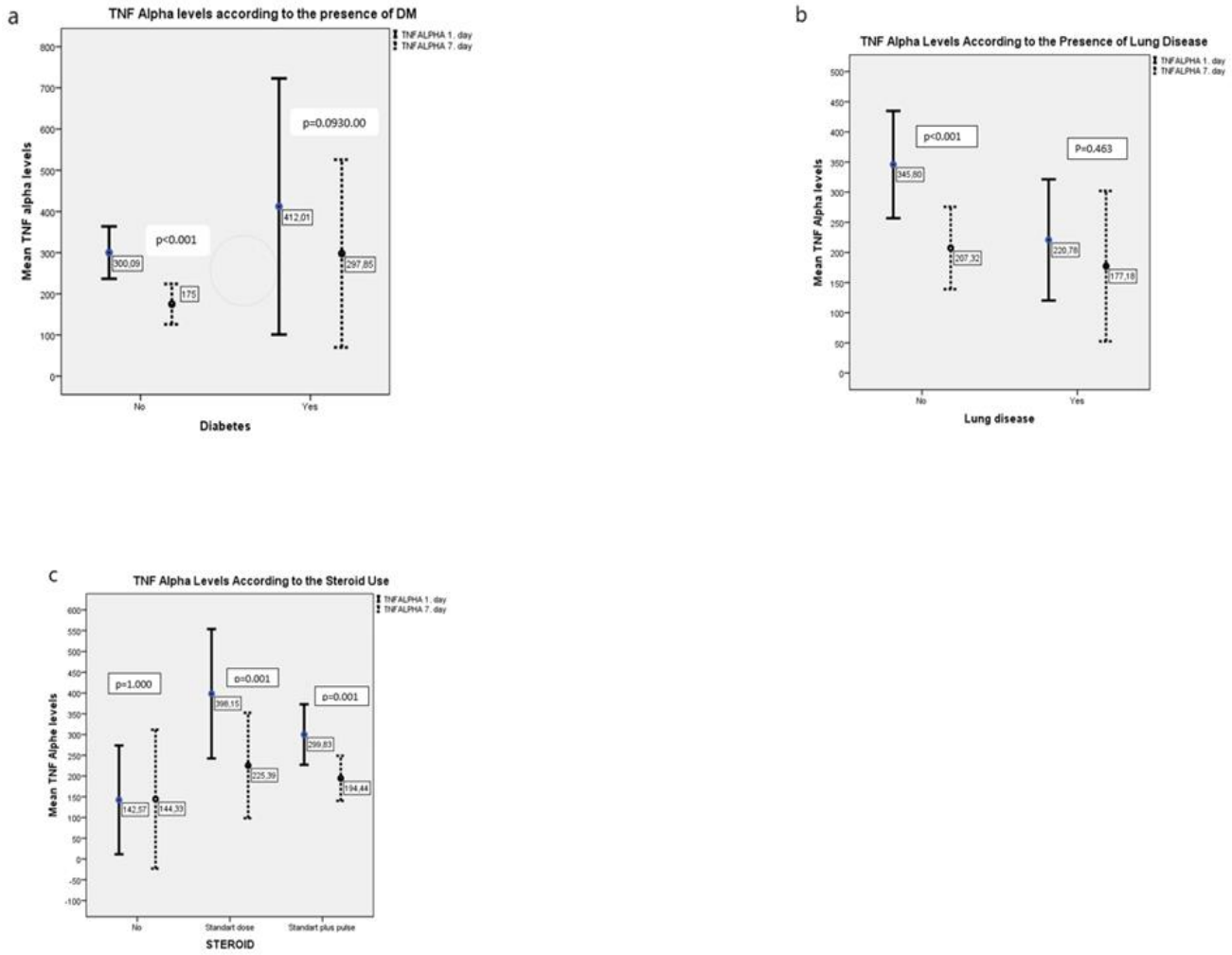

Figure 1. Diabetes mellitus (a), lung disease (b) and steroid use (c) effects the TNF-α decrease.

When the patients with and without hypertension and heart disease were evaluated, it was observed that the decrease in CRP and TNF-α was significant in both, ferritin decrease was found to be insignificant in both (Table 2).

When the relationship between disease symptoms and decrease in TNF-α CRP and ferritin is examined; While the decrease in and CRP was not significant in those with fever, the decrease was found to be significant in those without fever. While the decrease in and CRP was not significant in those without dyspnea, the decrease was found to be significant in those with dyspnea. While ferritin decreased significantly in those with fever, the decrease in ferritin was not significant in those without fever. While ferritin decreased significantly in those with cough, the decrease in ferritin was insignificant in those without cough (Table 3).

The decrease in TNF-α and CRP were insignificant in those who did not treated with steroids, while the decrease in TNF-α and CRP were significant in those who received steroids. Ferritin decrease was found to be insignificant in all groups (Table 4, Figure 1c).

Table 3. TNF-α, CRP and Ferritin changes according to initial symptoms

	Mean	SS	Median	Minimum	Maximum	p
Fever (+)						
TNF-α (Day 1)	370.3	128.2	426.0	113.7	499.9	0.018
TNF-α (Day 7)	217.2	152.8	258.2	36.1	440.8	
CRP (Day 1)	82.8	66.9	67.0	3.0	220.0	0.075
CRP (Day 7)	43.4	65.8	17.0	1.0	203.0	
Ferritin (Day 1)	275.6	198.0	322.0	49.0	591.0	0.011
Ferritin (Day 7)	415.0	322.9	448.0	35.0	1155.0	
Fever (-)						
TNF-α (Day 1)	306.6	233.8	307.2	28.5	1266.0	<0.001
TNF-α (Day 7)	198.7	179.6	199.1	15.9	930.1	
CRP (Day 1)	89.9	73.7	82.0	2.0	257.0	<0.001
CRP (Day 7)	26.9	30.4	16.0	0.7	115.5	
Ferritin (Day 1)	330.4	279.0	231.0	18.0	1037.0	0.544
Ferritin (Day 7)	421.9	369.6	269.4	15.0	1463.0	
Dyspnea (+)						
TNF-α (Day 1)	312.5	150.2	321.7	29.0	567.0	<0.001
TNF-α (Day 7)	189.3	130.0	202.7	15.9	440.8	
CRP (Day 1)	108.5	74.1	120.0	9.0	257.0	<0.001
CRP (Day 7)	30.5	43.8	16.0	0.7	203.0	
Ferritin (Day 1)	332.0	244.4	283.0	23.0	1010.0	0.232
Ferritin (Day 7)	421.2	359.2	382.0	15.0	1360.7	
Dyspnea (-)						
TNF-α (Day 1)	325.9	296.4	288.4	28.5	1266.0	0.028
TNF-α (Day 7)	225.2	235.0	180.1	23.6	930.1	
CRP (Day 1)	53.6	52.9	36.3	2.0	180.0	0.103
CRP (Day 7)	30.4	33.2	12.0	1.0	115.5	
Ferritin (Day 1)	294.5	302.1	179.3	18.0	1037.0	0.308
Ferritin (Day 7)	418.8	364.0	269.4	114.0	1463.0	
Cough (+)						
TNF-α (Day 1)	337.5	122.0	321.7	113.7	567.0	0.003
TNF-α (Day 7)	214.0	92.1	245.9	50.4	340.7	
CRP (Day 1)	76.5	73.3	28.5	2.0	192.0	0.019
CRP (Day 7)	37.6	52.9	14.0	1.0	203.0	
Ferritin (Day 1)	271.9	266.3	221.0	23.0	1010.0	0.012
Ferritin (Day 7)	462.2	424.9	351.5	15.0	1360.7	
Cough (-)						
TNF-α (Day 1)	304.4	268.2	309.0	28.5	1266.0	<0.001
TNF-α (Day 7)	192.9	219.3	132.7	15.9	930.1	
CRP (Day 1)	96.8	70.7	85.0	9.0	257.0	<0.001
CRP (Day 7)	25.1	27.2	16.0	0.7	115.5	
Ferritin (Day 1)	352.8	260.6	278.0	18.0	1037.0	0.685
Ferritin (Day 7)	389.0	300.9	275.8	57.0	1463.0	
Weakness (+)						
TNF-α (Day 1)	343.5	153.9	366.0	79.4	567.0	0.003
TNF-α (Day 7)	218.4	129.0	230.3	22.7	440.8	
CRP (Day 1)	95.1	71.9	93.0	2.0	233.0	0.003
CRP (Day 7)	31.2	46.0	16.5	1.0	203.0	
Ferritin (Day 1)	280.1	242.8	224.5	23.0	1010.0	0.126
Ferritin (Day 7)	326.3	248.4	257.0	15.0	1180.0	
Weakness (-)						
TNF-α (Day 1)	298.3	259.8	305.5	28.5	1266.0	<0.001
TNF-α (Day 7)	189.3	203.6	149.5	15.9	930.1	
CRP (Day 1)	82.4	72.6	77.0	3.5	257.0	0.001
CRP (Day 7)	29.7	34.5	16.0	0.7	115.5	
Ferritin (Day 1)	356.0	281.4	245.4	18.0	1037.0	0.398
Ferritin (Day 7)	514.5	424.3	448.0	35.0	1463.0	
Myalgia (+)						
TNF-α (Day 1)	342.0	131.9	369.2	113.7	438.3	0.043
TNF-α (Day 7)	181.8	96.4	195.5	50.4	273.7	
CRP (Day 1)	90.5	75.8	127.0	3.0	220.0	0.012
CRP (Day 7)	11.6	07.6	12.0	1.0	21.0	
Ferritin (Day 1)	384.6	336.4	322.0	23.0	1010.0	0.401
Ferritin (Day 7)	437.8	346.7	383.0	15.0	1180.0	
Myalgia (-)						
TNF-α (Day 1)	314.5	229.8	309.0	28.5	1266.0	<0.001
TNF-α (Day 7)	205.6	183.0	210.8	15.9	930.1	
CRP (Day 1)	88.1	71.8	78.0	2.0	257.0	<0.001
CRP (Day 7)	34.9	43.4	16.5	0.7	203.0	
Ferritin (Day 1)	303.9	246.7	231.0	18.0	1037.0	0.155
Ferritin (Day 7)	416.3	363.6	269.4	35.0	1463.0	

TNF-α: Tumor necrosis factor-alpha, CRP: C-reactive protein

Table 4: TNF-α, CRP and Ferritin changes according to steroid use

	Mean	SS	Median	Minimum	Maximum	p
Steroid (-)						
TNF-α (Day	141.6	92.5	199.6	28.5	255.2	1.000
TNF-α (Day	144.3	144.8	204.7	23.6	305.0	
CRP (Day 1)	56.2	63.9	82.8	3.5	162.1	0.144
CRP (Day 7)	29.0	26.9	32.1	2.0	54.4	
Ferritin (Day	264.3	324.6	145.5	23.0	743.1	0.285
Ferritin (Day	435.5	687.2	132.0	15.0	1463.0	
Steroid (80						
TNF-α (Day	383.8	275.4	373.8	79.4	1266.0	0.001
TNF-α (Day	225.4	237.4	184.1	22.7	930.1	
CRP (Day 1)	70.7	62.0	55.5	2.0	233.0	0.017
CRP (Day 7)	30.2	49.7	12.0	1.0	203.0	
Ferritin (Day	312.5	321.5	206.5	18.0	1037.0	0.379
Ferritin (Day	346.3	285.9	312.5	35.0	1180.0	
Steroid (250						
TNF-α (Day	299.8	158.7	321.7	29.0	567.0	0.001
TNF-α (Day	194.4	118.2	292.7	15.9	440.8	
CRP (Day 1)	111.4	76.5	120.0	9.0	257.0	0.001
CRP (Day 7)	30.9	34.9	16.0	0.7	115.5	
Ferritin (Day	334.9	201.6	253.0	55.0	765.0	0.122
Ferritin (Day	477.5	340.5	382.0	57.0	1360.7	

DISCUSSION

The present study investigated the factors that might affect TNF-α, CRP, and ferritin levels in inpatients diagnosed with COVID-19 during the pandemic. There was a significantly higher decrease in TNF-α levels in patients not diagnosed with diabetes mellitus (DM). Furthermore, the decrease in TNF-α and CRP levels was significant in patients without fever and patients using steroids, whereas the decrease in ferritin levels was not significant for patients under either of the above conditions.

Due to this cytokine storm, which occurs during COVID-19 infection, alternative treatments have started to be needed and the importance of anti-inflammatory drugs gradually increased. It turned out that anti-inflammatory drugs are just as important as antivirals. For this purpose, in the treatment of COVID-19, Interleukin (IL)-1 Receptor Antagonists, (IL)-6 Receptor Antagonists, Janus Kinase Inhibitors, Granulocyte-Macrophage Colony-Stimulation factor, Anti-tumorsis Factor-α, and corticosteroids were used (6).

In a study by Xiaobo Yang et al., the most prevelant comorbidities of the 32 non-survivors from a group of 52 intensive care unit patients diagnosed with COVID-19 included cerebrovascular diseases (22%) and diabetes (22%) (7). A related study investigated 1,099 patients, including 19 cases of confirmed COVID-19 and 173 cases with severe comorbidities of hypertension (23.7%), DM (16.2%), coronary heart disease (5.8%), and cerebrovascular disease (8). Zhang et al. reported hypertension in 30% and diabetes in 12% of patients (out of 140) admitted to the hospital with COVID-19 (9).

In a meta-analysis by Kumar et al., which investigated diabetes and disease severity in patients with COVID-19, the primary endpoint of the study was set as the relationship between diabetes with mortality and disease severity. The above study found that the probability of severe disease and mortality was two-fold higher in patients with diabetes. Therefore, patients with COVID-19 with concurrent diabetes are more susceptible to acute respiratory distress syndrome (ARDS), require extensive treatment in intensive care units and invasive ventilation, and are more vulnerable to mortality (10).

It was reported that interleukin 6 (IL-6) levels were higher in COVID-19 patients with diabetes compared to those without diabetes. Individuals with diabetes may be affected by low-grade chronic inflammation, which may facilitate cytokine storms associated with mortality in many patients suffering from COVID-19 (11,12).

A study, which investigated cytokine release from neutrophils in patients with type 2 diabetes found excessive TNF-α, interleukin 6 (IL-6), and interleukin 1β (IL-1β) release. Additionally, it was reported that this applied to stimulated conditions that increased sensitivity to both basal and invasive pathogens. Patients with diabetes had elevated M1 pro-inflammatory macrophage levels that contributed to local and systemic inflammation and released inflammatory mediators. The phenotypes and activity of natural killer (NK) cells are also subject to changes in diabetes. There are remarkable decreases in NK receptors that recognize the virus and receptors that activate NK cells and cytotoxic T lymphocytes (CD8 T). Hyperglycemia and hyperinsulinemia, accompanied with the stimulation of Advanced glycosylation end products, may induce the formation of a pro-inflammatory cytokine profile that may lead to maturation in dendritic cells (13).

Consistently, some retrospective studies compared COVID-19 patients with diabetes to patients without diabetes and found higher levels of CRP, TNF-α, procalcitonin, and neutrophil-lymphocytes in the former group (14). Continuous hyperglycemia in patients with diabetes induces a series of abnormal metabolic changes leading to impaired functioning of the immune system by increasing superoxide production and inflammatory pathway activation (15).

Studies report that TNF-α levels were higher in patients with severe disease compared with those with mild disease (5). Moreover, it was found that higher levels of soluble TNF-α receptors were associated with higher mortality in intensive care patients (16). In the present study, TNF-α values decreased at a lower rate in patients with diabetes compared with patients without diabetes. This may suggest that TNF-α levels are associated with disease severity in patients with DM.

The mechanism of TNF-α blockers affecting disease prognosis had not been established during the early stages of the Covid-19 pandemic. Some case reports emphasized that patients on TNF-α blockers due to rheumatological diseases were infected by Covid-19 during their treatment; nevertheless, there was no deterioration in disease prognosis. In fact, it was suggested that the use of other anti-inflammatory drugs for Covid-19 was beneficial in disease prognosis (17).Accordingly, TNF-α blockers may be considered in Covid-19 patients with DM, who develop excessive inflammation.

Efficacy of steroids as a treatment option for Covid-19 infections has been suggested in cases of hypoxemia (18). Cytokine upregulation has been confirmed in Covid-19; Covid-19 patients have elevated levels of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), TNF-α, and IFN-γ, and several cytokine concentrations are elevated in intensive care patients (19). In the current study, patients responded to steroid therapy in terms of inflammatory indicators as well as a decrease in CRP and TNF-α levels. Serum TNF-α levels increased moderately in SARS patients, where much higher levels in serum of patients with Covid-19 showed a positive correlation with disease severity. There is no adequate evidence to support anti-TNF-α antibody use as a potential treatment for Covid-19, although it has been recommended (20). The current study may shed light on further studies as it suggested that steroid therapy was associated with decreases in TNF-α levels.

A study by Baslılar S. et al., which retrospectively investigated 324 patients that received anti-TNF-α antibodies, reported that 44 (13.6%) patients were infected by Covid-19, yet no mortality was reported. Patients that required hospitalization had a higher rate of being diagnosed with DM. The study concluded that Covid-19 patients treated with anti-TNF-α antibodies might have a milder clinical course and better prognosis (21).

CONCLUSIONS

This study showed the TNF-α decrease in COVID-19 patients, affects from DM, lung diseases and steroid treatment.

Authors's Contributions: Idea/Concept: M.G., M.A., M.A., P.A.; Design: M.G., M.A., Ş.Y., N.E.Y., G.K.; Data Collection and/or Processing: M.G., M.A. Ş.Y., N.E.Y., M.A., G.K., P.A.; Analysis and/or Interpretation: M.G., M.A., P.A.; Literature Review: M.G., P.A.; Writing the Article: M.G., P.A.; Critical Review: M.G., M.A., Ş.Y., N.E.Y., M.A., G.K., P.A.

REFERENCES

1. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current tnf-α inhibitors in therapeutics. Int J Mol Sci. 2021; 22(5): 2719.
2. Karki R, Sharma BR, Tuladhar S, Williams EP, Zalduondo L, Samir P, et al. Synergism of TNF-α and IFN-γ triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. Cell. 2021; 184(1): 149-168.e17.
3. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest. 2020; 130(5): 2202-05.
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(5): 846-8.
5. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130(5): 2620-9.
6. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs. 2020; 80(13): 1267-92.
7. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475-81.
8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18): 1708-20.
9. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75(7): 1730-41.
10. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr. 2020; 14(4): 535-45.
11. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020; 36(7): e33213321.
12. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229): 1033-34.

13. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev. 2021; 37(2): e3377.
14. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care. 2020; 8(1): e001343.
15. Hameed I, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes. 2015; 6(4): 598-612.
16. Mortaz E, Tabarsi P, Jamaati H, Dalil Roofchayee N, Dezfuli NK, Hashemian SM, et al. Increased serum levels of soluble TNF-α receptor is associated with ICU mortality in COVID-19 patients. Front Immunol. 2021; 12: 592727.
17. Duret PM, Spielmann L, Messer L. Response to: 'Correspondence on recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. A report on a COVID-19 patient with psoriatic arthritis receiving ustekinumab' by Messina et al. Ann Rheum Dis. 2021; 80(5): e80.
18. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397(10285): 1637-45.
19. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet. 2020; 395(10234): 1407-09.
20. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020; 39(7): 2085-94.
21. Baslılar S, Pehlivan O. Evaluation of factors affecting the frequency and clinical course of COVID-19 in patients using anti-TNF-alpha agents. Rev Assoc Med Bras (1992). 2021; 67(9): 1286-92.