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Original paper

Serum levels of C-reactive protein and ferritin in COVID-19 patients infected with *Toxoplasma gondii*

Marwa Salim ALI, Entsar Jabbar SAHEB

Department of Biology, College of Sciences, University of Baghdad, Baghdad, Iraq

Corresponding Author: Marwa Salim Ali; e-mail: marwasalim815@gmail.com

ABSTRACT. During infection, *T. gondii* disseminates by the circulatory system and establishes chronic infection in several organs. Almost third of humans, immunosuppressed individuals such as HIV/AIDS patients, cancer patients, and organ transplant recipients are exposed to toxoplasmosis. Therefore, the study aimed to investigate the possibility that *Toxoplasma* infection could be a risk factor for COVID-19 patients and its possible correlation with C-reactive protein and ferritin. Overall 220 patients referred to the Al Furat General Hospital, Baghdad, Iraq were enrolled from 2020–2021. All serum samples were tested for *T. gondii* immunoglobulins (IgG and IgM) antibodies, C-reactive protein and ferritin levels. In patients with COVID-19, the results revealed a high positivity percentage for anti-*Toxoplasma* IgG. In COVID-19 patients infected with *T. gondii*, the C-reactive protein and ferritin levels were higher than the controls. The ferritin level was high in COVID-19 patients infected with toxoplasmosis compare with COVID-19 patient without toxoplasmosis in different gender and age while the level of CRP had no significant differences in COVID-19 patient with or without toxoplasmosis. These finding suggest that the incidental rate of toxoplasmosis could be considered as an indication to the high risk of COVID-19.

Keywords: *Toxoplasma gondii*, COVID-19, C-reactive protein, ferritin

Introduction

The protozoan *Toxoplasma gondii* infects all warm blooded animals, including humans, livestock, and marine mammals [1]. *T. gondii* infection is acquired primarily through ingestion of cysts in infected, undercooked meat or oocysts that may contaminate soil, water, and food meat [2]. The seropositivity level varies in different regions of the world, measuring between 30% and 60% in most countries [3]. During infection, *T. gondii* disseminates by the circulatory system and establishes chronic infection in several organs, including the heart and brain [4]. Almost third of humans, immunosuppressed individuals such as HIV/AIDS patients, cancer patients and organ transplant recipients are exposed to toxoplasmosis [5].

The coronavirus disease 2019 (COVID-19) is pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it has spread worldwide since its first recorded case in the city of Wuhan, China in December 2019. COVID-19 affects the respiratory tract, with the initial symptoms of common cold, fever, dry cough, fatigue, nasal congestion, sore throat and diarrhea to severe pneumonia, difficulty in breathing and ends with the patient death [6].

C-reactive protein (CRP) is a non-specific acute-phase protein induced by IL-6 in the liver and a sensitive biomarker of inflammation, infection, and tissue damage [7]. CRP expression level is usually low but increases rapidly and significantly during acute inflammatory responses [8]. The elevation of CRP in isolation or in combination with other markers may reveal bacterial or viral infections. A study explored the relationship between CRP and COVID-19 and found that patients with CRP>41.8 mg/l were more likely to develop severe disease [9]. The inflammatory response plays a critical role in COVID-19, and inflammatory cytokine storm increases the severity of COVID-19 [10].

Ferritin is an iron-storing protein; its serum level

Table 1. Serological examination of anti-*T. gondii* antibodies IgG and IgM in COVID-19 and control group

Antibodies	Control N=70		COVID-19 N=150		*P*-value
	No.	%	No.	%	
IgG (+)	25	35.71	50	33.33	0.473 NS
IgG (–)	45	64.29	100	66.67	0.473 NS
P-value	–	0.0035**	–	0.0029**	–
IgM (+)	2	2.86	0	0.00	0.581 NS
IgM (–)	68	97.14	150	100	0.581 NS
P-value	–	0.0001**	–	0.000z**	–

**$P \leq 0.01$, NS: non-significant

reverse the normal iron level and assistance the diagnosis of iron deficiency anemia. Circulation ferritin level rises during viral infections and can be a marker of viral replication [11,12]. Increased levels of ferritin due to cytokine storm and secondary hemophagocytic lymphohistiocytosis (s HLH) have been reported in severe COVID-19 patients [13].

Materials and Methods

Subjects and blood collection

This study was permitted by the Ethical Committee of Iraqi Ministry of Health, in which 220 blood samples were enrolled in this study and their age was between (20–60 years old). Seventy samples were taken from outpatient clinics as control groups. One hundred and fifty samples infected COVID-19 from Al Furat General Hospital in Baghdad, Iraq and outpatient clinics. Samples of 5 ml blood were taken from patients' vein. The samples were collected in sterilized Gel Clot activator vacuum tubes and left for 10 min at room temperature for clotting. Then, the samples were centrifuged at 3000 round per minute for 5 min then dispensed into Eppendorf- tubes and stored at –20ºC until the test day.

Serological tests

Specific IgG antibodies were measured using commercial *Toxoplasma* IgG and IgM EIA Test Kit (ACON Laboratories, Inc. USA) (I231-1091) (I231-1101) based on the principle of ELISA capture [14], according to the manufacturer's instructions. The serum C-reactive protein titer was measured by spin 200 devices and ferritin by using the vidas device

Table 2. The incidental rate of toxoplasmosis in control group and COVID-19 with different ages

Age	Control		COVID-19		*P*-value
	Toxo (–)	Toxo (+)	Toxo (–)	Toxo (+)	
20–30	17 (37.78%)	11 (44.00%)	32 (32.00%)	9 (18.00%)	0.0052**
31–40	13 (28.89%)	9 (36.00%)	18 (18.00%)	17 (34.00%)	0.731 NS
41–50	10 (22.22%)	3 (12.00%)	24 (24.00%)	13 (26.00%)	0.0325*
51–60	5 (11.11%)	2 (8.00%)	26 (26.00%)	11 (22.00%)	0.0309*
Total	45	25	100	50	–
P-value	0.0073**	0.0006**	0.0311*	0.022*	–

*$P \leq 0.05$, **$P \leq 0.01$, NS: non-significant

Table 3. The mean levels of C-reactive protein in control groups and COVID-19 patient according to toxoplasmosis

C-Reactive protein mg/l			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	2.34±0.09	2.73±0.12	0.872 NS
COVID-19 during infection stage	27.72±1.48	35.56 ±1.94	5.28*
COVID-19 after month	6.17±0.37	7.84±0.66	2.68 NS
LSD value	3.48**	5.21**	–

*$P \leq 0.05$, **$P \leq 0.01$, NS: non-significant

Table 4. The CRP means levels in males of COVID-19 patients according to toxoplasmosis

C-Reactive protein mg/l			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	2.28±0.13	1.79±0.06	0.933 NS
COVID-19	23.73±1.08	32.44±1.57	5.49 **
T-test	4.51**	5.09**	–

**$P \leq 0.01$, NS: non-significant

according to the manufacturing guidelines. The measurement ranges of the assay for C-reactive protein <=6.0 mg/l and ferritin for male 27–375 ng/ml while female 12–135 ng/ml.

Statistical analysis

Chi-square test was used to study the significant compare of the percentages and least significant difference – LSD test was used to significant compare between means in this study. Results are expressed as mean ± standard error of the mean. A *P*-value of less than 0.05 was considered significant.

Results

Serological examination of anti-T. gondii antibodies IgG and IgM in COVID-19 and control group

According to this study, the percentage of seropositive to anti-*Toxoplasma* IgG in COVID-19 patient was 33.33% and 35.71% seropositive to anti-*Toxoplasma* IgG of control group; there were no positivity rates for anti-*Toxoplasma* IgM in COVID-19 patients while the positivity rates for anti-*Toxoplasma* IgM among the control group was (2.86%) (Tab. 1).

The incidental rate of toxoplasmosis in control group and COVID-19 with different ages

The highest rate of toxoplasmosis in control group was in the age group 20–30 which was (44%) and lowest rate in age group 51–60 which was (8%) while the highest rate of toxoplasmosis in COVID-19 patients was in the age group 31–40 which was (34%) and lowest rate in age group 20–30 which was (18%) (Tab. 2).

C-reactive protein levels in COVID-19 patients and controls

The mean level of C-reactive protein in COVID-19 patients infected with toxoplasmosis during infection stage was (35.56±1.94 mg/l), being higher than the mean value in controls infected with toxoplasmosis which (2.73±0.12 mg/l (with a statistically significant differences ($P<0.01$). On the other hand, the mean level of C-reactive protein in COVID-19 patients infected with toxoplasmosis after month was (7.84±0.66 mg/l) (Tab. 3).

According to the mean levels of CRP in males and females with COVID-19 patients infected by *T.*

Table 5. The CRP mean levels in females of COVID-19 patients according to toxoplasmosis

C-Reactive protein mg/l			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	2.38±0.07	2.92±0.11	0.882 NS
COVID-19	19.78±0.83	19.57±0.79	1.49 NS
T-test	3.49**	2.61**	–

**$P \leq 0.01$, NS: non-significant

Table 6. The mean levels of ferritin in COVID-19 patients according to toxoplasmosis

Ferritin ng/ml			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	55.427±2.58	37.06±1.20	12.86**
COVID-19 during infection stage	241.024±14.61	294.87±13.74	23.67**
COVID-19 after month	165.18±8.66	209.02±8.32	22.16**
LSD value	31.94**	27.04**	–

**$P \leq 0.01$

gondii, the highest mean levels of CRP in males was (32.44±1.57 mg/l) compare with control group was (1.79±0.06 mg/l) while COVID-19 patient non-infected by *T. gondii* was (23.73±1.08 mg/l) with statically significant differences ($P<0.01$) (Tab. 4). In females infected with COVID-19 and *T. gondii* was (19.57±0.79 mg/l) compare with control group which was (2.92±0.11 mg/l) while COVID-19 patient non-infected by *T. gondii* was (19.78±0.83 mg/l), with no significant differences compare with COVID-19 patient infected by *T. gondii* (Tab. 5).

Ferritin levels in COVID-19 patients and controls

The mean level of ferritin in COVID-19 patients infected with toxoplasmosis was (294.87±13.74 ng/ml) during infection stage, being higher than the mean value in controls infected with toxoplasmosis which was (37.06±1.20 ng/ml) with a statistically significant differences ($P<0.01$) (Tab. 6). While mean level of ferritin in COVID-19 patients infected with toxoplasmosis after month (209.02±8.32 ng/ml) compare COVID-19 patients non-infected with toxoplasmosis was (165.18±8.66 ng/ml) with a statistically significant differences ($P<0.01$). According to different gender infected

Table 7. The ferritin means levels in males with COVID-19 according to toxoplasmosis

Ferritin ng/ml			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	93.42±4.37	63.74±2.50	11.27**
COVID-19 during infection stage	269.46±11.05	400.78±18.57	22.85**
COVID-19 after month	200.92±8.63	240.57±12.72	21.76**
LSD value	25.39**	31.96**	–

**$P \leq 0.01$

Table 8. The ferritin mean levels in females with COVID-19 according to toxoplasmosis

Ferritin ng/ml			
Studying groups	Toxo (–)	Toxo (+)	T-test
Control	36.42±1.09	30.40±1.15	5.09*
COVID-19 during infection stage	191.51±11.47	173.82±8.33	12.48*
COVID-19 after month	153.45±7.52	159.88±8.29	8.44 NS
LSD value	16.93**	14.88**	–

*$P \leq 0.05$, **$P \leq 0.01$, NS: non-significant

with COVID-19; the mean levels of ferritin in COVID-19 males infected with toxoplasmosis during infection stage was (400.78±18.57 ng/ml) compare with control group which was (63.74±2.50 ng/ml) with statically significant differences $P \leq 0.01$. While a month after the infection, COVID-19 patient males infected with *T. gondii* had (240.57 ±12.72 ng/ml) compare with COVID-19 patient not infected with *T. gondii* which was (200.92±8.63 ng/ml) with significant differences $P \leq 0.01$ (Tab. 7). In females, the mean levels of ferritin during infection stage was (173.82±8.33 ng/ml) lowest than those not infected with toxoplasmosis which was 191.51±11.47 ng/ml with statically significant differences $P \leq 0.05$ compare with control group (30.40±1.15 ng/ml). While a month after the infection, COVID-19 patient female infected with *T. gondii* had (159.88±8.29 ng/ml) compare with COVID-19 patient not infected with *T. gondii* which was (153.45±7.52 ng/ml) non-significant differences (Tab. 8).

Discussion

Toxoplasma gondii has been proposed as an important opportunistic pathogen in immuno-compromised patients [15]. Immunocompromised patients at greater risk for toxoplasmosis include those with hematologic malignancies particularly patients with lymphoma, or bone marrow transplant, or solid organ transplant or AIDS. A high seroprevalence rate of *Toxoplasma* infection among immunocompromised patients is about 50% [16]. On the other hand, some groups of immunocompromised patients appear to be at increased risk for severe COVID-19 disease [17]. In this study, the percentage of seropositive of anti-*Toxoplasma* IgG in COVID-19 patient was 33.33% which mean that about third of samples of COVID-19 infected with toxoplasmosis. *T. gondii* causes acute infection in immunosuppressive patients and the rate of infection is differed widely by many factors [18]. Incubation period of COVID-19 can extend from 2 to 14 days. Respiratory symptoms, which can range from mild to critically ill requiring mechanical ventilation, are the most common clinical feature of COVID-19 [19]. The Centers for Disease Control and Prevention (CDC) lists immunocompromised patients, including those requiring immuno-suppressive therapy following organ transplantation, as high risk for severe disease from SARS-CoV-2 [20].

COVID-19 shows an increased number of cases and a greater risk of severe disease with increasing age [22]. According to the current study, the highest rate of toxoplasmosis in patients with COVID-19 was in (31–40) year's old and lowest rate in (20–30) years old; it was recorded that the seroprevalence rate of toxoplasmosis increase with age [23]. A retrospective cohort study in China found that children and adults were just as likely to be infected. One key implication of this findings is that the incidence of fatalities from a COVID-19 outbreak depends crucially on the age groups that are infected, which in turn reflects the age structure of that population and the extent to which public health measures limit the incidence of infections among vulnerable age groups [24]. Even if an outbreak is mainly concentrated among younger people, it may be very difficult to prevent the virus from spreading among older adults. Age-varying susceptibility to infection by SARS-CoV-2, where children are less susceptible than adults to becoming infected on contact with an infectious person, would reduce cases among children [24]. Decreased susceptibility could result from immune cross-protection from

other corona viruses [25].

CRP is an essential component of the non-specific immune response, which is increased during infections and inflammation [26]. This study explored the relationship between CRP and COVID-19 and found that patients with CRP>41.8 mg/l were more likely develop severe disease. According to this study, after a month of infection and the disappearance of symptoms in a patient with COVID-19, CRP gradually returns to its normal state (7.84±0.66 mg/l) while patients not infected with toxoplasmosis (6.17±0.37 mg/l) consider non-significant. Females were more sensitive and more influence to *T. gondii* infection which has lowest CRP mean level than males. This result indicates that having low immune defense and unhealthy immune system become more sensitive to opportunistic infections. Several studies have investigated the association between depression and CRP according to gender, but the results are conflicting. An observation showed increased levels of CRP in men [27].

According to this, the mean level of ferritin in COVID-19 patients infected with *T. gondii* was raised. Ferritin levels decreased as CRP decreased during infection, but were significantly higher than the upper reference range for at least 5 days after hs-CRP returned to normal [28]. The ferritin in COVID-19 in male raise during infection and after month from infection. In inflammatory states there is a partial 'block' in the release of iron from the reticuloendothelial system and this is associated with an increased rate of ferritin synthesis [29]. The high concentration of ferritin in the liver means that damage leads to release of ferritin into the circulation [29]. Serum ferritin concentration are within the range 15–300 pg/l mean values are lower in women before the menopause than in men, reflecting lower iron stores caused by the iron losses of menstruation and childbirth [29]. The significance of serum ferritin estimations in iron deficiency [30] and iron deficiency anemia became established [31]. Anemia occurs as a result of infection with COVID-19. Numerous studies had shown that latent toxoplasmosis has important adverse effects on the mental and physical health of infected subjects [32]. *Toxoplasma*-infected subjects of both sexes had a more serious course of COVID-19. It was shown that toxoplasmosis represents a more pronounced risk factor for a severe course of COVID-19 than compromised autoimmunity, immunodeficiency, cat keeping, being overweight, higher age, or chronic obstructive pulmonary disease does [33].

This study shows a higher rate of *T. gondii* infection in COVID-19 patients. Thus, the incidental rate of toxoplasmosis could be consider as an indication to the high risk of COVID-19 due to the fact that the latent *Toxoplasma* infection leading to the compromised immunity of the patients. The level of C-reactive protein and ferritin were significantly higher in the COVID-19 with toxoplasmosis compare with control groups. The level of CRP has no significant differences in COVID-19 patient with toxoplasmosis or without while ferritin was high in COVID-19 patients infected with toxoplasmosis compare with COVID-19 patient without toxoplasmosis in different gender and age.

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