Advances in Bioscience and Bioengineering
2023; 11(2): 21-26
http://www.sciencepublishinggroup.com/j/abb
doi: 10.11648/j.abb.20231102.11
ISSN: 2330-4154 (Print); ISSN: 2330-4162 (Online)

The Role of Some Immunological and Hematological Aspects in Patients Infected with COVID-19 in Al-Anbar Province

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To cite this article:

Hazima Mossa Alabassi, Dhyauldeen Aftan Al Hayani, Omar Ismael Aljuamili, Anwar Khalil Ismael. The Role of Some Immunological and Hematological Aspects in Patients Infected with COVID-19 in Al-Anbar Province. *Advances in Bioscience and Bioengineering*. Vol. 11, No. 2, 2023, pp. 21-26. doi: 10.11648/j.abb.20231102.11

Received: June 30, 2023; **Accepted**: July 17, 2023; **Published**: July 26, 2023

Abstract: The study aimed to evaluate the immune response, its effect on the coagulant system and the outcome of infection with COVID-19 in two groups (convalescent & severe patients) and healthy individuals groups, 88 blood samples were collected (30 for convalescent and 30 for severe) and 28 for control. All patients with age range (19-70) years with COVID-19 mild and severe symptoms, attended at Ramadi city hospitals, from April 2020 to August 2020, (ELISA) technique was carried out to assess the serum levels of (IL-23 and IL-27) in addition to assess some of the coagulant factors such as ferritin, D-Dimer, CBC, Viral load (Anti SARS CoV-2 antibodies IgM and IgG), C-reactive protein and Erythrocyte sedimentation rate. The results showed that platelet observed decreasing levels in two patient groups (convalescent and severe compare with control). IgM recorded the high levels in severe cases which IgG high in convalescent cases, WBCs, Lymphocyte, Monocyte recorded a decreased count in severe and with no difference between convalescent and control, while Neutrophil count recorded a slight increase in convalescent when compared to controls, the cytokine IL-23 showed a highly significant increase in extreme and a significant increase in convalescent. Also, IL-27 recorded highly significant differences in severe and significant increases in convalescent compare with control. The coagulant factor system (ferritin, D-Dimer, ESR, and CRP) recorded a highly significant increase in severe compare with control, while in convalescent recorded a slight increase in serum levels of ESR and CRP with no difference in ferritin serum level, except D-Dimer which recorded a highly significant difference as compared with control, finally regard to gender male recorded the highest rate of infection as compared with female.

Keywords: COVID-19, Immunological, Hematological, IL-23, IL-27

1. Introduction

Coronavirus Disease -2019 (COVID-19), caused by the extreme acute respiratory coronavirus -2 (SARS CoV-2) has rapidly spread across the world in the last year. As of April 9, 2020, there have been 1,436,198 confirmed COVID-19 cases worldwide, with 85,522 deaths [1]. To date, the pandemic has cost the globe dearly in terms of human lives lost, economic costs, and increasing poverty [2, 3]. During the pandemic, Iraq had the highest number of confirmed, mortality, and recovered cases, and the number of confirmed COVID-19 cases increased dramatically beginning in July 2020 [4]. A severe acute respiratory syndrome is caused by COVID-19, a novel enveloped RNA β-coronavirus [5, 6].

Early stages in the SARS-CoV-2 infection, there may be no symptoms until severe pneumonia, dyspnea, organ dysfunction, and even death appear [7]. The majority of COVID-19 infections symptoms such as fever and cough are relatively mild, within 2-3 weeks of recovery (4-5), severe infections are characteristics with rapid progression to acute respiratory distress syndrome (ARDS), septic shock referred metabolic acidosis, coagulation disorder (by disseminated intravascular coagulation DIC), multi-organs failure and death [8]. A pathologic host response has been linked to COVID -19-related morbidity and mortality. There have been two opposing theories proposed. A hyper-inflammatory and cytokine storm mediating injury versus host protective immunity failure, resulting in viral spread and organ injury. The lack of diagnostic instruments to assess immune functions in COVID -19 infection has been a primary reason for the failure to overcome this controversy. It is unknown why a small proportion of patients experience serious illness, but it has been proposed that this results in both an overactive adaptive immune response and viral-induced lung pathology [9]. IL-23 (Interleukin -23) is a protein encoded by the IL-23 A gene [10], which is produced by Dendritic cells and Macrophages that considered as an important part of inflammatory response against infection, it increases angiogenesis and decreases CD8 T cell infiltration into tumors by promoting upregulation of the matrix metalloprotease [11]. IL-23 mediates innate and adaptive immune response, Th-17 represent the most pro-memory T cells subset that responds to IL-23, although IL-23 has been implicated in inhibitory the development of T- regulatory cells (T-reg) in the intestine, Th-17 produce IL-17 a pro-inflammatory cytokine that induces T-cells priming and stimulates the production of other pro-inflammatory such as IL-1, IL-6, tumor necrosis factor-alpha (TNF –α), nitric oxide synthase (NOS) and Chemokines [12]. IL-27 is a cytokine that has a variety of effects on the immune system. Although it was first linked to the production and development of the T1 response, it is now recognized as a powerful antagonist of various types of inflammation due to its ability to directly alter CD4+ and CD8+ T cells effector function to induce IL-10, and promote specialized T-reg cells response, Although this biological component of IL-27 has given insight into how the immune system prevents hypersensitivity in the context of infection and autoimmunity, as well as in cancer models and vaccination. IL-27 appears to have a strong stimulatory effect on CD8 T cell activity (en.Wikipedia.org). IL-27 is a member of the IL-12 superfamily of cytokine [13, 9]. IL-27 receptor A is highly expressed on T cells, IL-27 can stimulate the development of cytotoxic T lymphocytes by acting on CD8 T cells [13], maintain plasmacytoid dendritic cells (DC) [14], and block HIV replication in CD4 T cells [16]. IL-27 signaling leading to activate STAT 1 (signal transduction and activator 1 of transcription) and IRF -3 (Interferon Regulatory Factor -3) and suppress ZIK V infection keratinocytes, IL-27 acts as an activator of RNA virus effector proteins [10]. Our study research aimed to evaluate immune responses (humoral and cellular) to COVID-19 infections in order to develop more intervention strategies for patients with serious illness.

2. Material and Methods

A (88) Blood samples were collected, 28 sample from control and 60 sample from patients with age range (19-70 years old) with COVID-19 (convalescent and severe) symptoms who attended to Al- Ramadi Teaching Hospital, Al-Razzi Private Hospital, and private laboratories in Ramadi city (Al-Anbar province), according to the severity of infection and time of infection from April 2020 to August 2020. Serum was separated by centrifuged the blood samples (300 R. P. M) for 10 minutes, then frozen under -20 C° until used. ELISA technique was carried out to assessed the serum concentration of two pro-inflammatory cytokines IL-23 and IL-27 [17], in addition to some assays such as (D-Dimer by MINI-VIDUS BLUE), (Ferritin By TOSOH 600), (CBC such as platelet count, total WBCs and differential WBCs such as Lymphocytes, Monocytes, and neutrophils by Hb analyzer ERMA), Viral load (Anti -SARS CoV-2 IgM and IgG by MINI-VIDUS BLUE [18].

3. Statistical Analysis

The Statistical Analysis System- SAS (2012) program was used to detect the effect of different parameters in study. The least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significantly compare between means. Chi-square (χ^2) test was used to significantly compare between percentage (0.05 and 0.01 probability) in this study.

4. Results and Discussions

As shown in table 1 which demonstrated the comparison among the studied groups (severe cases, recovery cases, and control) according to Age and platelets count. the results that there were presented as mean ± SE, all severe cases with average Age 39.91 ±3.03 and platelet count 163.30 ±12.45.

Recovery patients with Age average of 41.87 ±3.28 and platelet count 246.26 ±20.72 as compared with control which with Age average of 44.70 ±4.85 and platelet count 252.10 ±32.63, there was no significant difference between the studied groups in terms of age, but there was a significant difference in platelet count. There is a significant decrease in platelet count between severe patients and control, This finding disagrees with a study performed [19] which recorded a significant increase in platelets count in patients with COVID-19 how admitted in an intensive care unit (ICU).

1. This decrease can be related to platelet apoptosis [20]. This also may explain by possible mechanisms of COVID-19 that associated with thrombocytopenia.
2. Activation by increased thrombin generation and consumption coagulopathy.
3. Platelets autoantibody formation, with subsequent platelet clearance.
4. platelets interaction activation associated with the

formation of platelet leukocyte aggregation,
5. FC (Receptor) mediated interaction with immune complex.
6. Platelets clearance due to increased endothelial damage.
7. Pulmonary vasculature – specific widespread damage.
8. Platelets activation and subsequent clearance by the reticuloendothelial system.
9. Due to direct viral infection.
10. Marrow/megakaryocytes suppression.
11. Splenic/hepatic sequestration.
12. Due to inflammatory response.
13. Due to reduced thrombopoietin.

In addition to the depletion of platelets through severe inflammation, as we know the platelet participate in inflammatory and immune response, they store multiple inflammatory molecules that upon release chemo attract innate immune cells, leukocytes and stimulate the endothelium, platelet can internalize pathogens and release microbiocidal proteins that kill certain bacteria and fungi that may be associated with virus infection.

Table 1. *Comparison among studied groups in age and Platelets.*

Group	Mean ± SE	
	Age (year)	Platelets
Sever cases	39.91 ±3.03	163.30 ±12.45 b
convalescent patients	41.87 ±3.28	246.26 ±20.72 a
Control	44.70 ±4.85	252.10 ±32.63 a
LSD value	10.68 NS	57.81 **
P-value	0.669	0.0016

This means having the different letters in the same column differed significantly. ** (P≤0.01).

Table 2 illustrates the comparison among studied groups according to levels of (IgM and IgG) serum level. IgM recorded the result which was as follow (4.83 ±0.56, 0.948 ±0.16 and 0.259 ±0.05) pg/ml, respectively with a highly significant increase in the severe patient compared with control and convalescent patients (P< 0.0001), also IgG recorded a highly significant difference among studied patients (P<0.0001) and recorded mean ±SE (0.480 ±0.06, 41.19 ±5.73 and 0.112 ±0.04) pg/ml, respectively, the highly increasing of IgM was recorded in severe patients while IgG recorded highly significant difference in convalescent patients. The Ab that produces the early immune response is IgM but if the infection is persistent, Isotype switching has occurred and IgG will be release which is more efficient for neutralizing the pathogen, the convalescent patients had a high serum level of IgG and this may be related to the elongation of its half-life. A study performed by Patrick, *et al* [18] recorded the high levels of IgG COVID-19 nucleocapsid specific antibody the median level for IgM, and the lowest level for IgA, in patients with pneumonia due to SARS CoV [21]. Anthony *et al*. [22] demonstrated a significant decrease (over 2.5 fold) of IgG levels in (ICU) patients, it has already demonstrated that seroconversion for IgG and IgM occurred simultaneously and that antibody titer plateaued and within 6 days often seroconversion. In contrast, mild non-ICU patients had a steady and yet robust rise in their specific IgG levels against COVID-19.

Table 2. *Comparison among studied groups in serum level of specific COVID-19 IgM and IgG Antibodies.*

Group	Mean ± SE	
	COVID IgM	COVID IgG
Sever cases	4.83 ±0.56 a	0.480 ±0.06 b
convalescent patients	0.948 ±0.16 b	41.19 ±5.73 a
Control	0.259 ±0.05 b	0.112 ±0.04 b
LSD value	1.460 **	9.337 **
P-value	0.0001	00001

This means having the different letters in the same column differed significantly. ** (P≤0.01).

Table 3 illustrates the comparison of Total WBCs count and differential count (Lymphocyte, Monocyte, and neutrophil) among the understudied groups. The results as follow for (severe, convalescent and control) (4.53 ±0.28, 0.758 ±0.07, 0.730 ±0.08 and 3.03 ±0.24) (9.37 ±0.79, 2.76 ±0.65, 0.973 ±0.08 and 5.83 ±0.56) in severe and convalescent patients, respectively as compared with control (8.33 ±0.73, 2.16 ±0.22, 1.39 ±0.18 and 4.78 ±0.49) there was a significant difference among the understudied groups (P<0.0001, 0.0004, 0.0006 and 0.0001), respectively. The total WBCs count decreased in severe patients compared with control while it was significantly increased in convalescent patients as compared with a control group. WBCs are associated with an increased risk of COVID-19, but the direction and nature of this association are unclear [23]. The decrease may be explained by the exhausting of WBCs through the infection, while the increase may be due to the increase of cytokines such as (IL-3, CSF-GM) that follow the exhaustion of the cell [24].

Table 3. *Comparison among studied groups in WBC and differential count.*

Group	Mean ± SE			
	WBCs	Lymphocytes	Monocytes	Neutrophils
Sever cases	4.53 ±0.28 b	0.758 ±0.07 b	0.730 ±0.08 b	3.03 ±0.24 b
convalescent patients	9.37 ±0.79 a	2.76 ±0.65 a	0.973 ±0.08 b	5.83 ±0.56 a
Control	8.33 ±0. 73 a	2.16 ±0.22 a	1.39 ±0.18 a	4.78 ±0.49 a
LSD value	1.675 **	1.097 **	0.315 **	1.227 **
P-value	0.0001	0.0004	0.0006	0.0001

This means having the different letters in the same column differed significantly. ** (P≤0.01).

Table 4 illustrates the comparison of cytokine levels (IL-23 and IL-27) in all the understudied groups. IL-23 was recorded as the mean levels for severe, convalescent & control groups (677.73 ±76.89, 175.73 ±17.77 and 21.80

±2.57) pg/ml, respectively, a significant difference among all the studied groups recorded (P<0.0001), while IL-27 recorded as the mean levels (431.05 ±32.41, 166.20 ±21.80 and 21.90 ±3.52) pg/ml, respectively. also, there was a significant difference among all the studied groups (P<0.0001). IL-23 serum level recorded a highly significant elevation in severe and convalescent patients compared with control, also IL-27 recorded a highly significant elevation in serum level in severe and convalescent patients as compared to control. IL-23 considers cytokine, the increasing levels consistent with its crucial role against infectious viruses, and can regulate both innate and adaptive immunity. There are no previous studies have addressed the immunological aspects particularly IL-23 in patients with COVID-19, except an Iraqi study conducted on patients with hepatitis B virus and recorded an elevation level of IL-23 serum level in patients (unpublished data). IL-27 act on native CD8+ T cell to enhance the generation of cytotoxic T lymphocyte [13] maintain plasmacytoid dendritic cells [15], and block HIV viral replication in CD4+ T cells [15], IL-27 play a role as antiviral effector protein of RNA viruses [25, 10].

Table 4. *A Comparison among studied groups in serum level of IL-23 and IL-27.*

Group	Mean ± SE	
	IL-23	IL-27
Sever cases	677.73 ±76.89 a	431.05 ±32.41 a
convalescent patients	175.73 ±17.77 b	166.20 ±21.80 b
Control	21.80 ±2.57 b	21.90 ±3.52 c
LSD value	196.54 **	89.39 **
P-value	0.0001	0.0001

This means having the different letters in the same column differed significantly. * (P≤0.05).

Table 5 illustrates the comparison among the studied groups according to levels of (ferritin, d-dimer, CRP and ESR), there were a highly significant differences among the understudied groups in ferritin serum levels, The results for the (severe cases, convalescent and control) were (523.30 ±62.70, 92.41 ±15.27 and 93.00 ±16.55), respectively, (P<0.0001) the highly significant increasing level was in severe cases, while there were no significant differences between convalescent and control, for d-dimer, also there were a highly significant difference among all understudied groups, the results were (681.86± 173.43, 255.80 ±50.21 and 72.10 ±11.26), respectively, the highly increasing levels was recorded in severe patients, follow with convalescent cases compared with control group (P<0.0105), CRP was recorded a highly significant difference among all the studied groups, the results were (50.62± 4.09, 13.31± 156,3.37± 0.41), respectively, the highly increasing was recorded in severe patients follow with convalescent as compared with control (P 0.000). Finally, ESR was also recorded a highly significant among all understudied groups, the results were (54.69 ±4.53, 26.06 ±3.59, and 22.60 ±3.85), respectively, the high increase was recorded in severe patients, follow with recovery cases compared with control (P<0.0001). In our study, we found that an elevation in serum levels of the hemostatic – system (ferritin, d-dimer, CRP, and ESR) in severe cases, the increasing reach to more than 5 fold ferritin, 9 fold for d-dimer, 16 fold for CRP, and finally 2 fold for ESR. This increase may lead to a hypercoagulable state, a condition that commonly encounters sepsis also proportion for micro- thrombi formation in pulmonary small vessels of patients with severe COVID-19 infection is high. Regarding the convalescent patients, the increase in serum levels of coagulation state was as follows ferritin recorded no difference, d-dimer recorded 3.5 fold than control, CRP with 4.3 fold while ESR recorded a slight elevation. CRP is another acute–phase reactant that increases during the acute phase response [26]. D-Dimer is significantly increased in COVID-19 [27-29] likely reflecting pulmonary vascular bed thrombosis and fibrinolysis [30], D-Dimer reflects fibrin clot formation, clot cross-linking by factor FXIIIa, and fibrinolysis. The marked elevation of D-Dimer in COVID-19 appear to reflect coagulation activation from viremia and cytokine storm, but superinfection and organ temporally increasing D-Dimer level indicate progressive severity in COVID-19 infection, and can be used as a predictor that more critical care will be needed [26, 31].

Table 5. *A Comparison among all studied groups in serum level of Ferritin, d-dimer, CRP, and ESR.*

Group	Mean ± SE			
	Ferritin	d-dimer	CRP	ESR
Sever cases	523.30 ±62.70 a	681.86± 173.43 a	50.62 ±4.09 a	54.69 ±4.53 a
convalescent patients	92.41 ±15.27 b	255.80 ±50.21 ab	13.31 ±1.56 b	26.06 ±3.59 b
Control	93.00 ±16.55 b	72.10 ±11.26 b	3.37 ±0.41 b	22.60 ±3.85 b
LSD value	161.42 **	446.15 **	10.67 **	13.52 **
P-value	0.0001	0.0105	0.0001	0.0001

*This means having the different letters in the same column differed significantly. ** (P≤0.01).

Table 6 demonstrates the distribution of samples according to gender the results showed that percentage of infected male with severe infections was 14 (60.87%), while the recovery was 11 (73.33%). there were a significant difference between two groups (P<0.0028) and the percent of an infected female with severe infection was 9 (39.13%) and the convalescent was 4 (26.67%). there is no significant difference between the two groups, while there is a significant difference between the two genders in two groups (severe and convalescent cases) (P≤0.01), so according to this finding, it has been revealed that the rate of male infection was more than female. Jin *et al.* [32] who founded that men's cases tended to be more serious than women (P=0.035) and the number of men who died from COVID -19 is 2-4 times that

of women (70-3 vs 29-74 P=0.035), so this finding agrees with our finding but they conclude that, while men and women have the severe prevalence, men with COVID-19 are more at risk for worse outcome and death independent age.

Table 6. *Distribution of samples in different groups according to gender.*

Variables		Severe cases No. (%)	convalescent patients No. (%)	P-value
Gender	Male	14 (60.87%)	11 (73.33%)	0.0028 **
	Female	9 (39.13%)	4 (26.67%)	
	Total	23	15	---

** (P≤0.01).

5. Conclusion

Our finding which shown in severe patients did not support the routine use for corticosteroids in COVID-19 despite that some limiting suggest that the corticosteroid may reduce the mortality rate in COVID -19 patients but must be combined with anticoagulant therapy and the finding in recovery patients suggest that patients must be under vision until these factors will return to their normal state.

Finally, concerning gender, our findings suggest that the rate of male infection is more than female.

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