Hematological and Immunological Laboratory findings after Recovery from COVID-19 infection

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Abstract

Background: During the past few months, many countries encountered high prevalence of COVID-19 infection so it was needed to assess the severity of the disease and mortality in order to control this pandemic .There is a great requirement to detect the changes in different hematological and immunological markers during infection and after recovery from COVID-19 for better understanding of the disease in order to improve its prognosis and its effect on human body. Up to our knowledge, there is no such previous study at Faculty of Medicine Zagazig University (Egypt).

Aim: To assess changes in some hematological and immunological parameters after recovery from infection for better understanding of COVID-19 and to study the relationship between the studied parameters with COVID-19 disease severity and patient demographic data .

Subjects and methods: This is a prospective comparative cross sectional study. It was conducted in Clinical Pathology and Chest Departments, Faculty of Medicine, Zagazig University Hospitals (Egypt) on forty-five subjects who were previously diagnosed COVID-19 and achieve recovery ,they were divided into 3 groups, in addition to fifteen apparent healthy adult volunteers that matched well with the patients as regard age and sex.Hematological and immunological laboratory tests were measured for all participants.

Results: There were statistically significant differences among the studied groups regarding WBCs,D-dimer , most Liver and kidney function tests,Serum Electrolytes (sodium, potassium, magnesium, phosphorous) , Ferritin , IgA, C reactive protein, and antiphospholipid antibodies.and non-significant differences were found as regard tohemoglobin, platelet count , coagulation profile, urea, albumin, bilirubin, LDH,calcium, C3 , C4 , RF, IgM, and IgGhowever IgG and IgM are higher in patients groups than control group

Conclusion: Several hematological and immunological parameters may remain affected even after recovery from COVID-19 and the degree of impact on these parameters can be related to the severity of the disease and to the health condition of the patient.

Keywords: COVID-19, IgA, antiphospholipid, WBCs.

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1.0 Introduction

Since late 2019, a novel coronavirus originated in Wuhan causingan epidemic pneumoniaand spread rapidly all over China, then evolve to a global pandemic **[1].**

Formerly; it was kwon as new coronavirus 2019 (2019-nCoV), then WHO renamed it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On January 30, 2020, WHO declared SARS-CoV-2 epidemic as aninternational public health emergency. Coronaviruses are a large family that includes various types of viruses such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV) **[2].**

Coronaviruses are composed ofsingle-stranded RNA genome which is positive-sense and a helical capsid, both are enveloped within a lipid bilayer. analysis of COVID-19 genome Sequence showed strong homology to SARS-like coronaviruses which usually infect bats, and so , there is strong believe that this pandemic is of zoonotic origin **[3].**

Although the outbreak is thought to have started as a result of zoonotic transmission, recent reports proved that infection can transmit from person to person within in the same family also in hospital settings via directcontact or through droplets spread by coughing from an infected subject. Most patients infected with COVID-19 have slight or moderate manifestations and recover when receive the appropriate medical intervention(s). However, 15–32% havea severe or critical COVID-19 disease with a fatality rate of 1–15 % **[4].**

Nowadays; it is clearthat hematological markers and inflammatory indexes which depend on assessmentof the blood cell have an important value to predict the prognosis of infectious and non-infectious diseases **[5].**

Severe COVID-19infection has been accompanied with many laboratory features such as low lymphocytic count, increased C-reactive protein (CRP), high D-dimer and liver enzymes. also, hematological markers and indexes for example; neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were tested as potential indicators for COVID-19 infectionseverity**[1].**

SARS-CoV-2virus genome consists of single-strandedRNA which is positive-sense and it gets access into human cells via through angiotensin-converting enzyme 2 (ACE2) **[6].**

Usually, various mechanisms of immune system function to sense all stages of viral reproduction and to save the human body against the virus attack. The pattern recognition receptors ofinnate immunity functionto recognizethe antigen of the virus and the virus-induced damage, stimulating hematopoiesis by the bone marrow to release myeloid cells in peripheral bloodespecially neutrophils and monocytes, which produce many cytokines and chemokines**[7].**

If the duration and amplitude of released inflammatory mediator is not controlled then "emergency hematopoiesis" results ina cytokine storm and tissue damage which is manifested by organ dysfunction. Initial studies suggest that COVID-19infection is accompanied by occurrence of cytokine storm occurs**[8].**

Neutrophilia, lymphopenia and resulting elevated neutrophil / lymphocyte ratio (NLR), elevation of interleukin-6 (IL-6), and CRP correlate with rate of intensive care admission and fatality. Hence, detailed study of inflammatory mediators on the cellular and molecular level is valuableduring COVID-19 infection course;it could enhance to develop more effective medical interventions**[4].**

In the struggle against COVID-19 during thepandemicthat occurred all over the world, assessment of various clinical and laboratory parameters which help to predictprogressionto severe and fatal disease forms was urgently required. These parameters would be valuable to stratifyrisk, and help interventional studies to identify patients which are high risk to develop severe form of the disease and assist to save the few human and technical resources during the pandemic. Also, characterization of laboratory markerswhich are able to differentiate between severe and non-severe patients, or who are at low or higher mortality risk, would help improvement of clinical awareness**[9].**

COVID-19 infection still causes significant disease and deaths all overthe worldwith rapid spread. In the same time, a test which is quick, reliable and easy has not been discovered to diagnose the disease. So it is very important to assess the changes in the routine laboratory values, which are easier, faster to reach, and more valuable both in the diagnosis and to assess prognosis**[10].**

2.0 Subjects and Methods

This is a prospective comparative cross sectional study. It was performed in Clinical Pathology and Chest Departments, Faculty of Medicine, Zagazig University Hospitals (Egypt) during the period from July 2021 to February 2024. Informed consent was obtained from all participants and the study protocol was authorized by the Zagazig University Institutional Review Board(Egypt) (ZU-IRB # 7056). The study was done according to the Code of Ethics of World Medical Association (Declaration of Helsinki).

Sixty subjects were included in this study and grouped as the following:

- **Patients groups**: Forty-five adult patients previously diagnosed as COVID-19 and achieved recovery according to recovery criteria that include: normalization of temperature for more than 3 days, significant improvement of respiratory symptoms together with significant absorption of lung lesions as shown by CT chest imaging, and on doing RNA test at least two consecutive negative results 24 hours apart are reached**[11]**.

Patients with evidence of COVID-19 infection indicated by laboratory and radiological findings, age 18 years or more were included in the study.

patients less than 18 years, patients who are still hospitalized for COVID-19 sequalae, patients still on oxygen therapy at home after recovery and patients with chronic diseases or on drugs that can affect measured parameters were excluded from the study.

They were subgrouped into:

1. **Group I:** included 15 Patients who are recovered from COVID-19 from 1-3 months.
2. **Group II:** included15Patients who are recovered from COVID-19 from 3 – 6 months.
3. **Group III:** included15Patients who are recovered from COVID-19 from ≥ 6 months.
    - **Control group**: fifteen apparent healthy adult volunteers that matched well with the patients as regard age and sex .

All investigations were done after one month, 3 months and 6 months of recovery (as stated by treating physician according to recovery criteria).

All subjects included in this study were subjected to:

1. Full history taking.
2. Clinical examination.
3. Laboratory investigations including :

- **Complete blood picture (CBC)** Was performed on automated cell counter Xn 2000 (sysmex , Japan) using an EDTA samples.
- **Erythrocyte Sedimentation Rate (ESR)**Was measured by ESR analyzer VB0125 (Shenzhen Yhlo Biotech Co., China) using an EDTA samples .
- **Coagulation profile : PT , PTT ,and Fibrinogen**, testswere done on automated blood coagulation analyzer, model CS 2100 (Sysmex , Japan) using citrated plasma
- **D-dimer** was done byautomated turbidimetric immunoassay using Cobas 6000 autoanalyzer, (Roche diagnostic , Switzerland) using citrated plasma

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- **Liver and kidney function tests , LDH, serum electrolytes,Ferritin and CRP :** were done on Cobas 8000 autoanalyzer (Roche diagnostic , Switzerland) by using serum samples .
- **Complement components (C3 and C4), Immunological markers (IgA , IgM , IgG) and Rheumatoid Factor (RF)** were done on Cobas 6000 autoanalyzer,(Roche diagnostic , Switzerland) using serum samples.
- **Antiphospholipid antibodies (APL):** serum samples were tested for Anti-phospholipid Antibodies using Human anti-phospholipid antibody IgG(Apl/APA-IgG) using ELISA kit (INNOVA BIOTECH) which depends on Sandwich-ELISA technique. The Microelisa strip plate which is provided in the kit is pre-coated with a specific antigen to Apl/APA-IgG. Which binds tothe specific antibody present in standards or samples when added to the sutibleMicroelisa stripplate wells. After that; a Horseradish Peroxidase (HRP)-conjugated antigen specific for Apl/APA is added to each well and incubated. Un bound substances are washed. Then add TMB substrate solution to each well. Only

those wells that contain Apl/APA-IgG and HRP conjugated Apl/APA antigen will be colored blue then become yellow upon addition of stop solution. Finally;The optical density (OD) is measured by spectrophotometer at a wavelength of 450 nm. The presence of Apl/APA-IgG is detected by comparison with the cutoff value.

Statistical analysis

Data were analyzed using (Statistical Package for the Social Sciences) softwareSPSS version 26. Variables which are categorical were described using their absolute and relative frequencies and there comparison was done using chi square and Monte Carlo tests when suitable. Quantitative variables were described using their means and standard deviations or median and range according to type of data. Shapiro-Wilk test was used to assess normality.Kruskal Wallis test was usedto comparemore than two groups of non- normally distributedquantitative data while one way ANOVA test was used for comparison of more than two groups of normally distributed data. When therewas a significantdifference, we usedpairwise comparison to evaluate relationships between pairs of means and Fisher LSD comparison to calculate the smallest significant difference between two meansin order to assess difference between each two individual groups.To test correlation between two continuous variables ofnon-normally distributed dataand assess its strength and direction Spearman rank correlation coefficients was used. Linear regression analysis was performed to measure associated independent factors for dependent factor. The level of statistical significance was set at $P<0.05$. Highly significant difference was present if $p\leq0.001$.

3.0 Results

This study included 45 patients who recovered from COVID-19 infection and 15 healthy subjects as control group

Patients group included 24 females and 21 males,**their ages ranged from 18-85 years old, they were sub grouped into**

1. **Group I:** included 15 Patients who are recovered from COVID-19 from 1-3 months.
2. **Group II:** included15Patients who are recovered from COVID-19 from 3 – 6 months.
3. **Group III:** included15 Patients who re recovered from COVID-19 from ≥ 6 months.

By comparing the demographic data of studied groups, we found that there is statistically non-significant difference between them as regarding age or gender. Female represented 46.7%, 66.7%, 46.7% and 73.3%, where male represented 53.3% , 33.3% , 53.3% and 26.7% within group I, II, III and Control Group respectively as shown in ***table 1***. The history of the presenting symptoms of the patients groups show statistically non-significant difference either fever, malaise/headache, pharyngitis/sore throat, loss of smell/taste, dry cough or abdominal symptoms as described in ***table (1)***.In the same table we shows that there was statistically non-significant difference between the studied patients groups regarding COVID-19 severity based on O2 saturation and CT positive findings.

Comparison between the groups as regard CBC shows that there is statistically non-significant difference in hemoglobin and platelet count, howeverthere is statistically significant difference between the studied groups regarding white blood cell count and on doing differential leucocyticcount Statistically significant differences were found between studied groups as regard : neutrophils , Lymphocytes , Eosinophils , Basophils and monocytes. On doing posthoc LSD comparison, the difference is significant between group I and control group. On doing pairwise comparison, the difference is significant between control group and each other group as follow:

- As regard neutrophils : there were statistically significant differences between control group and each of patients groups; group I (P5 = 0.001) , group II (P6 < 0.001) , group III (P3 = 0.012).

- As regard Lymphocytes: there is statistically significant difference between group I and Group III (P4 = 0.012), control group and group II (P6 < 0.001).
- For Eosinophils, Basophils, and, monocytes: there were statistically significant differences between control group and group III (P3), control group and Group I (P5), control group and group II (P6)as shown in ***table (2)*** .

As regard liver and kidney functions , we conclude that there is statistically significant difference between the studied groups regarding Creatinine. On doing posthoc LSD comparison, the difference is significant between each two groups. There is statistically non-significant difference between the studied groups regarding urea. There is statistically significant difference between the studied groups regarding total protein. On doing posthoc LSD comparison, the difference is significant between control group and each other group . There is statistically significant difference between the studied groups regarding AST and ALT. On doing posthoc LSD comparison, the difference is significant between each two groups. There is statistically non-significant difference between the studied groups regarding albumin,direct, or total bilirubin (***Table 3***).

Table (4)shows that there is statistically non-significant difference between the studied groups regarding serum **calcium**. There is statistically **significant** difference between the studied groups regarding serum **Magnesium,Potassium , Sodium and Phosphorus** and on doing posthoc LSD comparison, Magnesium and Potassiumshow significant difference between group III and both groups I and II. also, there is significant difference between groups I and Control Group . On doing posthoc LSD comparison for serum Sodium, the difference is significant between each two groups except when comparing group III and Control Group and on doing posthoc LSD comparison for serum Phosphorus , the difference is significant between Control Groupand each other group .

Our results demonstrated there is statistically non-significant difference between the studied groups regarding Prothrombin Time (PT), International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT) or Fibrinogen. However, there was a statistically **significant** difference between the studied groups regarding D dimer. On doing pairwise comparison, the difference is significant between group I and both II and control group ***(Table 5).***

Analyzing the inflammatory markers show that IgA, CRP and Ferritin were significantly higher in patients groups than control group and on doing pairwise comparison for IgA;the difference is significant between group III and both II and control group and also between control group and group I. For CRP; the difference is significant between control group and each other group . For ferritin; the difference is significant between group II and both III and control group and also between groups I and both III and control group .There were statistically non-significant differences between the studied groups regarding RF , C4, C3, IgG, IgM , ESR or LDH although IgG and IgM are higher in patients groups than control groupas described in***table (6)***.

Antiphospholipid Antibodies (APL) level was tested in the serum of the study participants and it was positive in five patients (33.3%) within group I, three patients (20%) within group II and two patients (13.3%) within group III and was negative within control group and there was no significant difference between the studied groups***(table 7)*** . There was statistically significant negative correlation between APL and hemoglobin level (table 8, figure 1). Also, there is statistically significant positive correlation between APL and both D dimer and fibrinogen***(table 8, figure 2&3).*** On the other hand, there is non-significant correlation between APL and either other CBC parameters, liver, kidney function test, coagulation profile or serum electrolytes as shown in ***table (8)***. There is statistically significant positive correlation between APL and all of RF, CRP,C3, IgA, ESR, and serum LDH***(table 9, figures 4-9).*** There is statistically non-significant positive correlation between APL and all of IgG, IgM and C4, also there is statistically non-significant negative correlation between APL and ferritin ***(Table 9).***

Finally, Among factors significantly correlated to APL, CRP (unstandardized β=0.003, p=0.006), fibrinogen (unstandardized β=0.23, p<0.001) and C3 (unstandardized β=0.003, p=0.023) significantly independently associated with it ***(Table 10).***

Table (1) Comparison between the studied groups regarding demographic data, history of presenting symptoms and severity of COVID-19based on O2 saturation and CT findings during infection:

	Group I N=15	**Group II N=15**	**Group III N=15**	**Control Group N=15**	**χ^2**	**P**
Gender:						
Female	7 (46.7%)	10 (66.7%)	7 (46.7%)	11 (73.3%)	3.497	0.321
Male	8 (53.3%)	5 (33.3%)	8 (53.3%)	4 (26.7%)		
Age (year)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**F**	**P**
	42.87 ± 16.12	45.27 ± 14.59	45.47 ± 19.9	44.53 ± 14.63	0.077	0.972
	Median(Range)	**Median(Range)**	**Median(Range)**	**Median (Range)**		
	41 (18-73)	**45 (24-78)**	**42 (21-85)**	**44(21-71)**		
History of presenting symptoms	**Group I N=15 (%)**	**Group II N=15 (%)**	**Group III N=15 (%)**	**χ^2**	**P**	
Fever	9 (60%)	11 (73.3%)	8 (53.3%)	1.324	0.516	
Malaise/ Headache	3 (20%)	8 (53.3%)	4 (26.7%)	4.2	0.122	
Pharyngitis	3 (20%)	6 (40%)	2 (13.3%)	MC	0.4	
Loss of smell/ Taste	2 (13.3%)	3 (20%)	2 (13.3%)	MC	>0.999	
Dry cough	5 (33.3%)	7 (46.7%)	6 (40%)	0.556	0.757	
Abdominal pain/diarrhea	2 (13.3%)	3 (20%)	2 (13.3%)	MC	>0.999	
COVID-19 seerity						
O2 saturation	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	1.268	0.292	
	82.4 ± 18.56	89.8 ± 12.98	90.2 ± 13.1			
CT evidence of lung infilteration	10 (66.6%)	8 (53.3 %)	7 (46.6%)	1.142	0.263	
Severity						
Mild	4 (26.7%)	6 (40%)	5 (33.3%)	MC	0.733	
Moderate	6 (40%)	6 (40%)	8 (53.3%)			
Severe	5 (33.3%)	3 (20%)	2 (13.3%)			

SD: standard deviation, **F**: One way ANOVA test, **χ^2**: Chi square test, **MC**: Monte Carlo test

Table (2) Comparison between the studied groups regarding CBC parameters:

	Group I N=15	Group II N=15	Group III N=15	Control Group N=15	F	P
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**		
Hemoglobin(g/dl)	11.78 ± 1.43	12.59±1.86	12.69±1.52	12.47±1.12	1.125	0.347
Platelet count(10^3/mm^3)	277.53 ± 105.15	288.13 ± 97.2	260.4 ± 110.64	278.33 ± 97.13	0.189	0.904
WBCs(10^3/mm^3)	12.88 ± 4.9	10.48 ± 3.73	10.95 ± 5.32	8.15 ± 2.42	3.143	0.032*
LSD	P_1 0.127	P_2 0.761	P_3 0.076	P_4 0.219	P_5 0.003*	$P_6$0.139
	Median(IQR)	**Median(IQR)**	**Median(IQR)**	**Median(IQR)**	KW	P
Neutrophil	7.2 (1.4 – 10)	4.9(2.3 –6.3)	3.1(1.2 – 4.7)	4(3.3– 8)	4.328	<0.001**
Pairwise	P1 0.253	P2 0.821	P3 0.012*	P4 0.221	P5 0.001**	P6<0.001**
Lymphocyte	0.3(0.1 – 0.7)	0.9(0.1 – 1.1)	2.2(0.5 – 4)	3.1(1.6 – 5.2)	2.365	<0.001**
Pairwise	P1 0.631	P2 0.452	P3 0.124	P4 0.012*	P5 0.112	P6<0.001**
N/L ratio	0.3(0.2 – 0.5)	0.5(0.2 – 0.6)	0.6(0.2 – 0.8)	0.9(0.1 – 1.4)	5.137	0.112
Eosinophil	12.14(8.6- 17.75)	10.5(8.1– 15.7)	12(4.8 – 17.7)	3.5(2.2 – 4)	24.817	<0.001**
Pairwise	$P_1$0.427	$P_2$0.917	P_3<0.001**	P_4 0.668	$P_5$0.001**	P_6<0.001**
Basophil	0.7(0.5 – 0.9)	0.9(0.7 – 1)	0.8(0.5 – 0.9)	1.6(1.4 – 2)	35.917	<0.001**
Pairwise	P_1 0.197	P_2 0.216	P_3<0.001**	$P_4$0.958	$P_5$0.001**	P_6<0.001**
Monocytes	10(7.5 – 14.2)	8.2(7.3 – 11)	7.9(4.3 – 13.1)	6(4.5 – 7.2)	13.563	0.003*
Pairwise	P_1 0.301	P_2 0.818	$P_3$0.021*	P_4 0.206	$P_5$0.001**	$P_6$0.011*

WBCs: white blood cells, **N/L:** neutrophil/ lymphocyte, **SD:** standard deviation, **IQR**: Interquartile Range, **F:**One way ANOVA test,**KW**:Kruskal Wallis test, **LSD**: Least significant difference , *****:p<0.05 is statistically significant, ****:** p <0.001is highly significant, **p1:** difference between group I and II , **p2**: difference between group II and III , **p3**: difference between group III and Control Group , **p4**: difference between group I and III , **p5**:difference between group I and control group, **p6**: difference between group II and control group.

Table (3) Comparison between the studied groups regarding renal and liver function test:

	Group I N=15	Group II N=15	Group III N=15	Group IV N=15	F	P
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**		
Creatinine (mg/dl)	1.18± 0.1	0.919± 0.13	0.72± 0.24	0.58 ± 0.16	37.87	<0.001**
LSD	P_1 0.004*	P_2<0.001**	P_3<0.001**	P_4 0.001**	P_5 0.001**	P_6<0.001**
Urea (mg/dl)	12.9(10.9 – 14.4)	12.6(11 – 19)	11.1(10.9 – 14.4)	14.8(11.25 – 19.1)	2.754	0.431
Total protein(g/dl)	6.66 ± 0.42	6.61 ± 0.41	6.65 ± 0.75	7.38 ± 0.8	5.283	0.003*
LSD	P_1 0.839	P_2 0.857	P_3 0.002*	P_4 0.981	P_5 0.002*	P_6<0.001**
Albumin (g/dl)	3.51 ± 0.54	3.89 ± 0.49	3.73 ± 0.75	4.03 ± 0.28	2.558	0.064
AST (u/l)	39.85 ± 9.29	27.86 ± 5.89	21.89 ± 7.34	13.65 ± 2.14	40.647	<0.001**
LSD	P_1<0.001**	P_2 0.018*	P_3<0.001**	P_4<0.001**	P_5<0.001**	P_6<0.001**
ALT (u/l)	39.67 ± 5.99	29.8 ± 4.77	25.7 ± 4.81	16.19 ± 3.08	62.292	<0.001**
LSD	P_1<0.001**	P_2 0.022*	P_3<0.001**	P_4<0.001**	P_5<0.001**	P_6<0.001**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**KW**	**P**
Direct bilirubin(mg/dl)	0.1(0.1 – 0.2)	0.16(0.1 – 0.2)	0.1 (0.1 – 0.21)	0.12(0.1 – 0.23)	0.148	0.985
Total bilirubin (mg/dl)	1.1(0.9 – 1.7)	0.8(0.47 – 1.1)	0.57(0.19 – 1.1)	0.95(0.85 – 1.13)	4.902	0.179

AST: aspartate transaminase, **ALT:** alanine transaminase, **SD:** standard deviation, **IQR**: Interquartile Range, **F:**One way ANOVA test,**KW**:Kruskal Wallis test, **LSD**: Least significant difference , *****:p<0.05 is statistically significant, ****:** p <0.001is highly significant, **p1:** difference between group I and II , **p2**: difference between group II and III , **p3**: difference between group III and

Control Group , **p4**: difference between group I and III , **p5**:difference between group I and control group, **p6**: difference between group II and control group.

Table (4) Comparison between the studied groups regarding electrolytes:

	Group I N=15 (%)	Group II N=15 (%)	Group III N=15 (%)	Control Group N=15 (%)	F	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Calcium (m/g/dl)	9.01 ± 1.07	9.47 ± 0.83	8.95 ± 0.56	9.57 ± 0.47	2.533	0.066
Magnesium(mg/dl)	1.73 ± 0.26	1.85 ± 0.22	2.19 ± 0.35	2.01 ± 0.2	8.635	<0.001**
LSD	P_1 0.225	P_2 0.001**	P_3 0.079	P_4<0.001**	P_5 0.004*	P_6 0.086
Potassium(mmol/l)	3.92 ± 0.46	4.11 ± 0.29	4.27 ± 0.46	4.37 ± 0.56	2.962	0.04*
LSD	P_1 0.249	P_2 0.322	P_3 0.541	P_4 0.035*	P_5 0.007*	P_6 0.112
Sodium (mmol/L)	131.93 ± 5.42	135.8 ± 3.17	140.2 ± 2.51	139.6 ± 2.95	16.203	<0.001**
LSD	P_1 0.006*	P_2 0.002*	P_3 0.658	P_4<0.001**	P_5<0.001**	$P_6$0.007*
Phosphorus	2.67±0.61	2.83±0.65	3.09±0.55	3.6±0.58	6.833	0.001**
LSD	P_1 0.465	P_2 0.249	P_3 0.024*	$P_4$0.063	P_5<0.001**	$P_6$0.001**

SD: standard deviation, **F:**One way ANOVA test,**LSD**: Least significant difference , *****:p<0.05 is statistically significant, ****:** p <0.001is highly significant, **p1:** difference between group I and II , **p2**: difference between group II and III , **p3**: difference between group III and Control Group , **p4**: difference between group I and III , **p5**:difference between group I and control group, **p6**: difference between group II and control group.

Table (5) Comparison between the studied groups regarding coagulation profile:

	Group I N=15 (%)	Group II N=15 (%)	Group III N=15 (%)	Control Group N=15 (%)	F	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
PT	13.15 ± 1.59	13.08 ± 1.14	12.83 ± 0.89	12.56 ± 0.68	0.835	0.48
INR	1.05 ± 0.14	1.0 ± 0.13	1.07 ± 0.12	0.99 ± 0.09	1.428	0.244
APTT	35.09 ± 4.32	34.76 ± 4.24	34.38 ± 5.03	35.25 ± 3.2	0.124	0.946
Fibrinogen	3(2.2 – 4.1)	3.1(2.2 – 3.5)	2.9(2.4 – 3.8)	2.98(2.8 – 3.66)	0.411	0.938
D-dimer	0.4(0.3 – 0.5)	0.3(0.1 – 0.5)	0.3(0.2 – 0.4)	0.3(0.2 – 0.4)	7.995	0.046*
Pairwise	P_1 0.011*	P_2 0.453	$P_3$0.573	$P_4$0.075	P_5 0.019*	P_6 0.852

PT: Prothrombin time, **INR**: International Normalized Ratio, **APTT** : Activated Partial Thromboplastin Time, **F**:One way ANOVA test . *****:p<0.05 is statistically significant, ****:** p <0.001is highly significant, **p1:** difference between group I and II , **p2**: difference between group II and III , **p3**: difference between group III and Control Group , **p4**: difference between group I and III , **p5**:difference between group I and control group, **p6**: difference between group II and control group.

Table (6) Comparison between the studied groups regarding immunological and inflammatory markers:

	Group I N=15 (%)	Group II N=15 (%)	Group III N=15 (%)	Controlgroup N=15 (%)	KW	P
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**		
RF (IU/ml)	13(11.5 – 22)	16(13 – 19)	15(12 – 23)	14(10.3 – 18.2)	2.522	0.471
C4 (mg/dl)	30.5(20.5 – 47)	33(22.3 – 40.2)	26(20.4 – 40)	36(20 – 40)	1.055	0.788
C3 (mg/dl)	119(95 – 179)	150(100.4 – 169)	96(89 – 166)	146(99 – 169)	2.521	0.472
IgG (g/L)	14(10.5 – 17.6)	14.5(11.6 – 16.6)	14.8(13 – 16)	10.8(7.2 – 14.4)	6.923	0.074
IgM (g/L)	2(1.5 – 2.1)	1.7(1.5 – 2.1)	1.9 (1.5 – 2.1)	1.12(0.8 – 2.2)	3.825	0.281
IgA (g/L)	2.5(1.8 – 3.2)	2.1 (1.8 – 2.8)	3.2 (2.1 – 4)	1.54 (0.91 – 2.6)	13.998	0.003*
Pairwise	P_1 0.335	P_2 0.017*	P_3<0.001**	$P_4$0.153	P_5 0.029*	P_6 0.223
ESR (mm/hr)	5(3.5 – 90)	15(10 – 19.8)	16(12 – 25)	19(15 – 24)	2.887	0.409
Ferritin (g/L)	0.6(0.430 – 0.640)	0.496(0.427 – 0.540)	0.240(0.220 – 0.290)	0.197(0.995 – 0.286)	0.0352	<0.001**
Pairwise	P_1 0.91	P_2 0.002*	$P_3$0.31	P_4<0.001**	P_5<0.001**	P_6 0.001*
CRP (mg/dl)	6.1(5.3 – 102)	6.5(5.05 – 19)	10.2(6.9 – 54)	3.66(2.5 – 5)	20.907	<0.001**
Pairwise	P_1 0.726	P_2 0.128	P_3<0.001**	$P_4$0.242	P_5 0.001**	P_6 0.004*
LDH (U/L)	200(180 – 290)	190(180 – 290)	190(154 – 247)	199.5(184 – 220)	2.203	0.531

RF: rheumatoid factor, **C:** complement, **Ig:** immunoglobulin, **ESR:** erythrocyte sedimentation rate, **CRP:** c-reactive protein, **LDH:** lactate dehydrogenase, **IQR**: interquartile range,**KW**: Kruskal Wallis test,*****:p<0.05 is statistically significant, ****:** p <0.001is highly significant, **p1:** difference between group I and II , **p2**: difference between group II and III , **p3**: difference between group III and Control Group , **p4**: difference between group I and III , **p5**:difference between group I and control group, **p6**: difference between group II and control group.

Table (7) Comparison between the studied groups regarding Anti Phospholipid Antibodies (APL):

	Group I N=15 (%)	Group II N=15 (%)	Group III N=15 (%)	Control group N=15 (%)	χ^2	P
Positive	5 (33.3%)	3 (20%)	2 (13.3%)	0 (0%)	MC	0.033
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	KW	P
Value U/ml	0.1(0.075– 1.87)	0.087(0.05 – 1.3)	0.18(0.02 – 1.7)	0.32(0.02 – 0.92)	1.742	0.628

IQR: interquartile range, χ^2: Chi square test,**K:W**Kruskal Wallis test , **MC:** Monte Carlo test

Table (8) Correlation between APL and laboratory data among studied patients:

	R	P
Hemoglobin (g/dl)	**-0.351**	**0.006***
Platelet count(10^3/mm^3)	-0.002	0.987
WBCs (10^3/mm^3)	0.103	0.434
Creatinine (mg/dl)	-0.092	0.484
Total protein(g/dl)	-0.186	0.156
Albumin (g/dl)	-0.137	0.295
Urea (mg/dl)	0.095	0.47
ALT (U/L)	-0.026	0.845
AST (U/L)	-0.018	0.894
Direct bilirubin(mg/dl)	0.237	0.069
Total bilirubin (mg/dl)	0.107	0.418
PT	0.068	0.605
INR	0.141	0.281
APTT (Sec)	0.228	0.08
D dimer (g/dl)	0.334	0.009*
Fibrinogen (g/dl)	0.532	<0.001**
Calcium (m/g/dl)	0.118	0.368
Magnesium(mg/dl)	-0.012	0.929
Potassium(mmol/l)	-0.101	0.44
Sodium (mmol/L)	-0.026	0.842
Phosphorus	0.128	0.329

WBCs: white blood cells **AST:** aspartate transaminase, **ALT:** alanine transaminase **PT**: Prothrombin time, **INR**: International Normalized Ratio, **APTT**: Activated Partial Thromboplastin Time, **R:** Spearman rank correlation coefficient,*p<0.05 is statistically significant, ****:** p <0.001is highly significant

T**able (9) Correlation between APL and immunological parameters among studied patients:**

	R	P
RF (IU/ml)	0.432	0.001**
C4 (mg/dl)	0.233	0.073
C3 (mg/dl)	0.491	<0.001**
IgG (g/L)	0.194	0.138
IgM (g/L)	0.075	0.571
IgA (g/L)	0.306	0.018*
ESR (mm/hr)	0.341	0.008*
Ferritin (Ug/L)	-0.034	0.795
CRP (mg/dl)	0.304	0.018*
LDH (U/L)	0.355	0.005*

RF: rheumatoid factor, **C:** complement, **Ig:** immunoglobulin, **ESR:** erythrocyte sedimentation rate, **CRP:**C-reactive protein, **LDH:** lactate dehydrogenase**R:** Spearman rank correlation coefficient,*p<0.05 is statistically significant, ****:** p <0.001is highly significant

Table (10) Linear stepwise regression analysis of APL among studied participants:

	Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval	
	β	Std. Error	Beta			Lower	Upper
(Constant)	-0.760	0.190		-4.000	<0.001**	-1.140	-0.379
Fibrinogen(g/L)	0.230	0.059	0.402	3.892	<0.001**	0.112	0.349
CRP(mg/dl)	0.003	0.001	0.294	2.856	0.006*	0.001	0.004
C3(mg/dl)	0.003	0.001	0.244	2.338	0.023*	0.000	0.005

CRP:C-reactive protein , **C:** complement *: $p<0.05$ is statistically significant **: $p\leq0.001$ is statistically highly significant

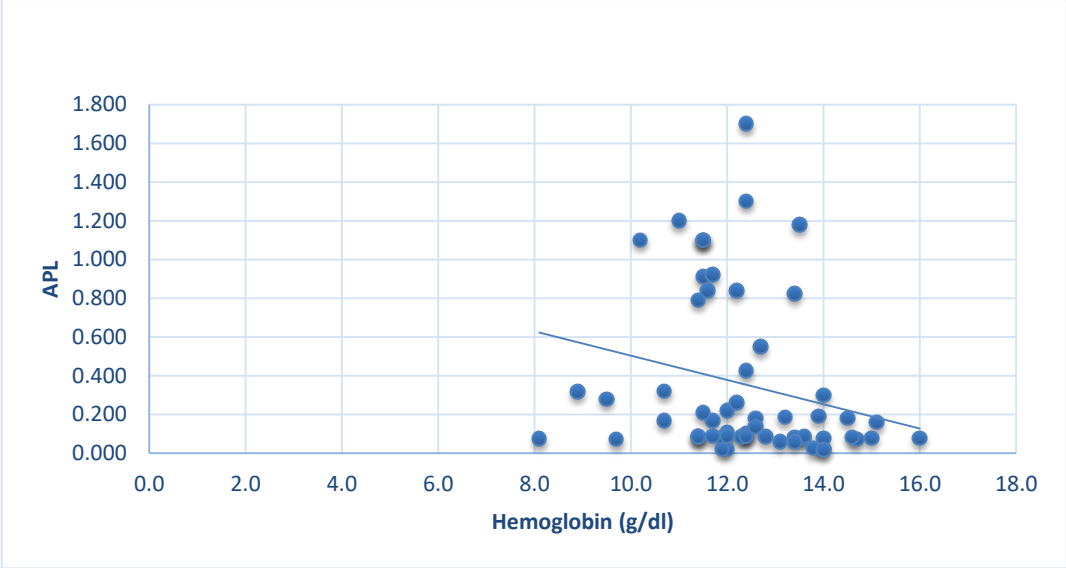

Figure (1) Scatter dot plot showing significant negative correlation between APL and hemoglobin

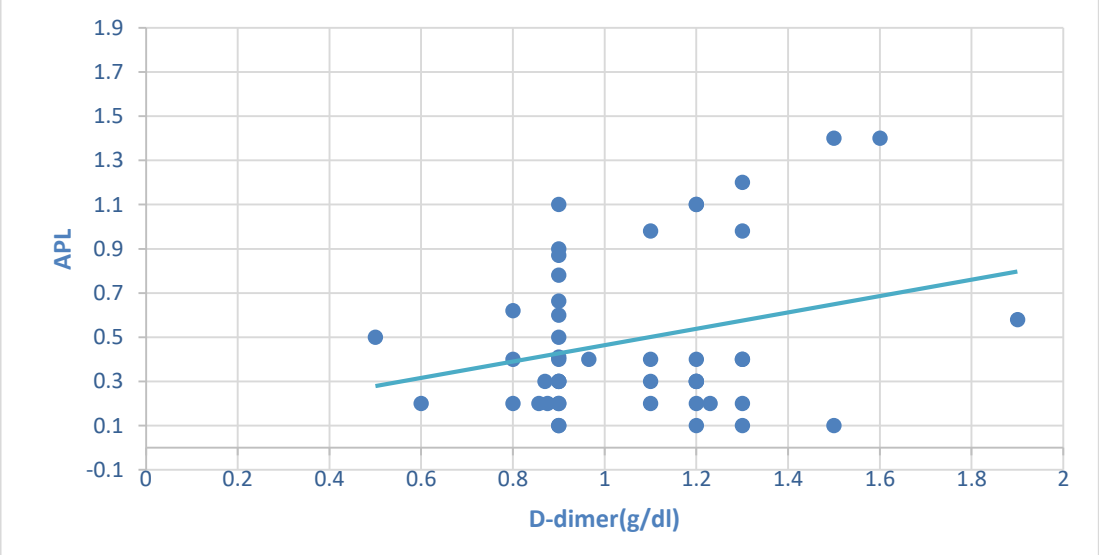

Figure (2) Scatter dot plot showing significant positive correlation between APL and D dimer

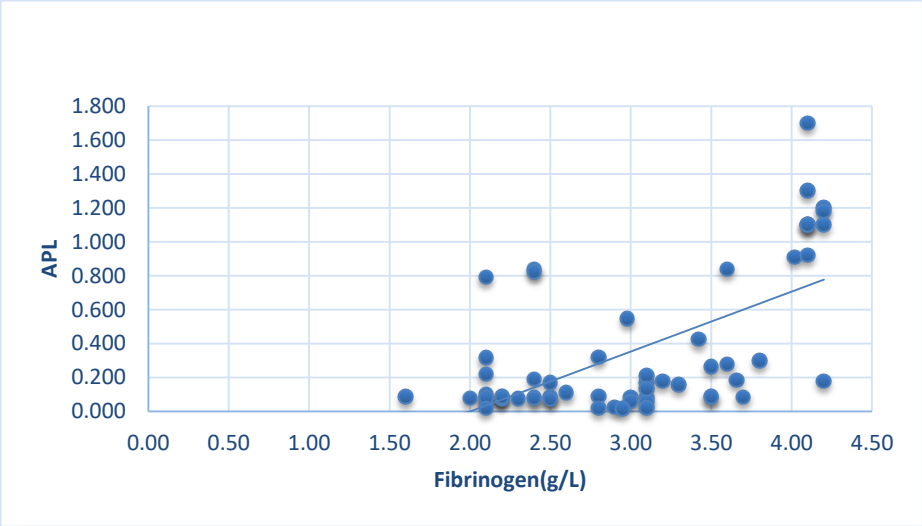

Figure (3) Scatter dot plot showing significant positive correlation between APL and Fibrinogen

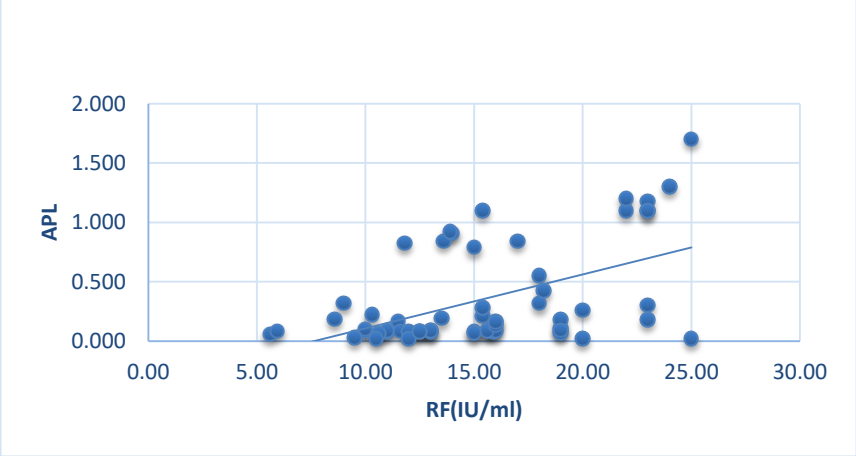

Figure (4) Scatter dot plot showing significant positive correlation between APL and RF

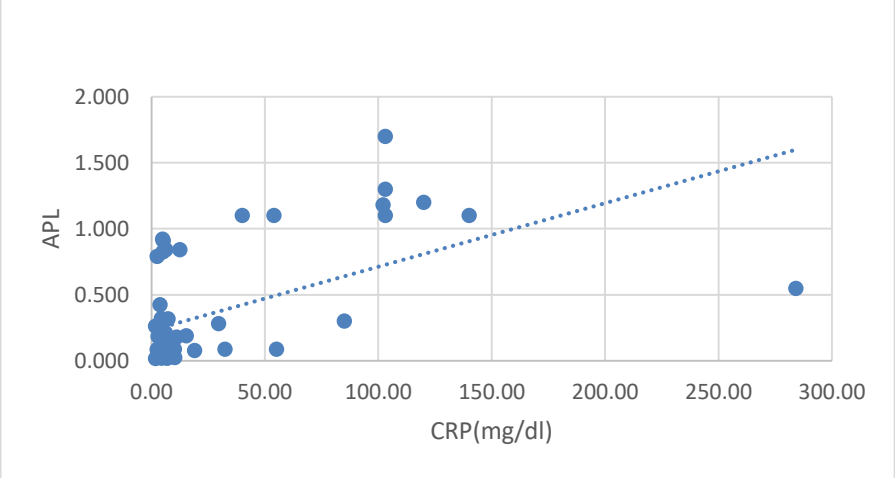

Figure (5) Scatter dot plot showing significant positive correlation between APL and CRP

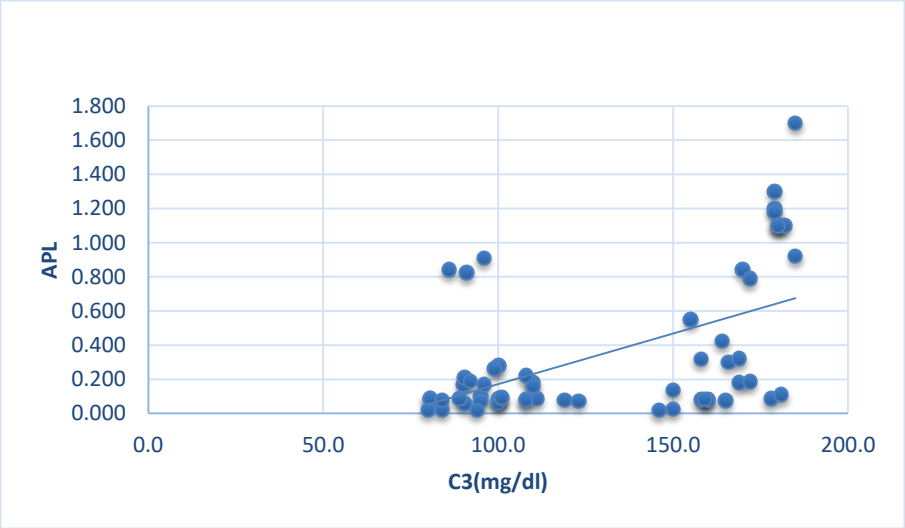

Figure (6) Scatter dot plot showing significant positive correlation between APL and C3

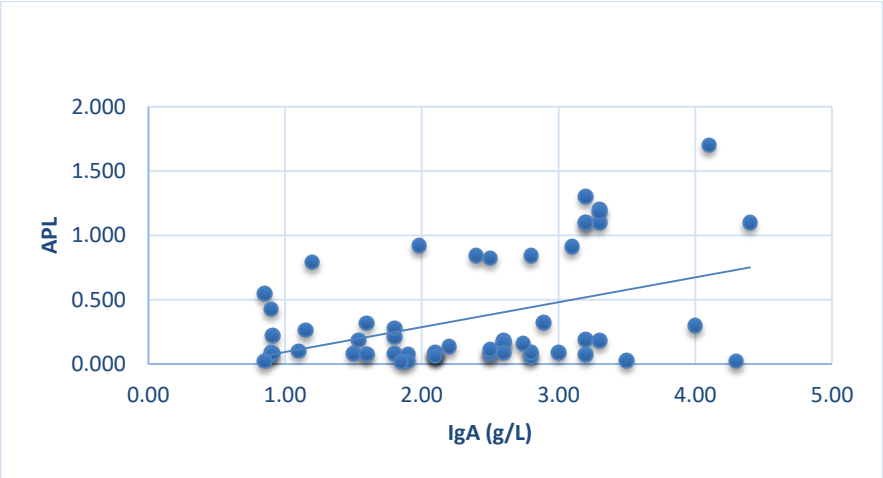

Figure (7) Scatter dot plot showing significant positive correlation between APL and IgA

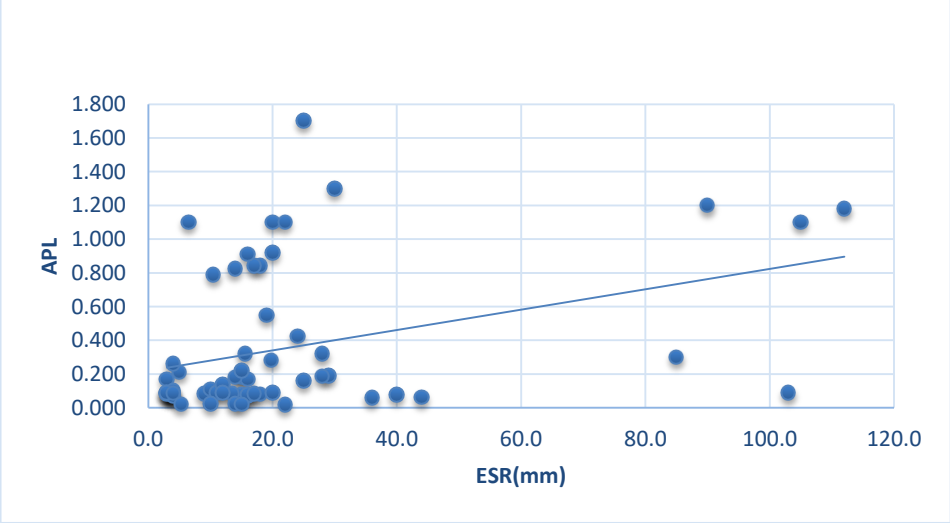

Figure (8) Scatter dot plot showing significant positive correlation between APL and ESR

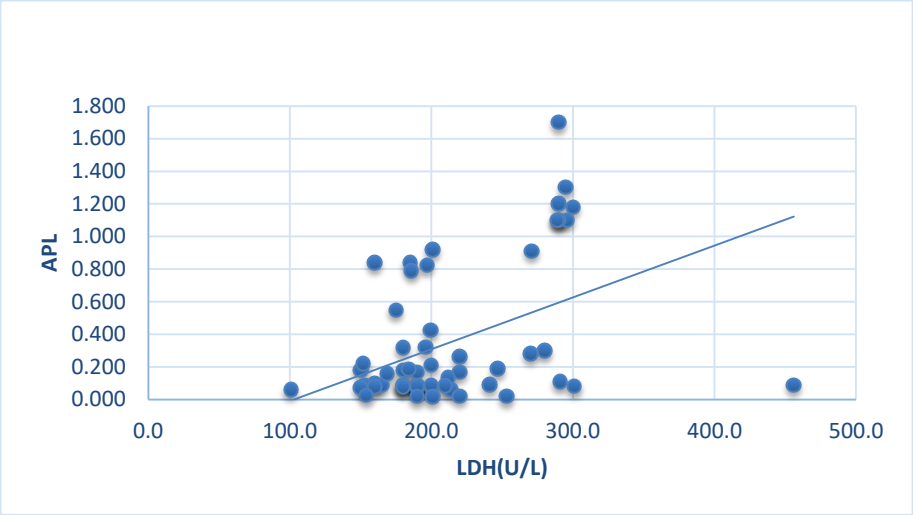

Figure (9) Scatter dot plot showing significant positive correlation between APL and LDH

4.0 Discussion

There is strong evidence thatvarious symptoms persistin patients after recovery from (COVID-19) which is known as 'long COVID' or 'post-COVID syndrome' (PCS) **[12].**

markers associated with severity of COVID-19 disease such as IL-6, IgG, anticardiolipin autoantibodies (aCL), eosinopenia and haemogram-derived ratios have been described in disease acute phase **[6].** However no biological markers have been established to predict PCS. So we did this study to find out changes in some hematological and immunological parameters after 1 month , 3 months and 6 months of COVID-19 infection in group of patients included in the study .

In this study the mean age was 42.87 , 45.27 and 45.47 in the three studied groups of patients recovered from COVID-19 infection compared to healthy control group with mean age 44.53.

Our result demonstrated that there is no statistically significant difference between the studied groups regarding age or gender. Male was more predominant in group I and III , but there isn´t statistically significant difference between groups and control group as regard gender . Female represented 46.7%, 66.7%, 46.7% and 73.3% within group I, II, III and control group respectively.

In agreement with our results,**Gameilet al. [13]**showed that the mean age of cases was 38.29±5.27 and upon comparing to healthy control subjects with mean age 37.25±4.87 there was no significant difference. As regard to gender it was matched among all participants. Male subjects represent 55.8% and 57.5% of case and control groups, respectively without significant difference (P=0.695).

Also,**Suryawanshi et al. [14]** showed that the median age of the 300 studied patients was 67 years ranged from 30-92 years;males represented 49.1% of the studied subjects withnon- significant differences between the studied groups as regard to the median age and sex ratios (P > 0.05).

In the current study, there is statistically non-significant difference between the studied groups regarding history of presenting symptoms; Fever represent 60% , 73.3% and 53.3% , dry cough represent 33.3% , 46.7% and 40% .Malaise/headache represent 20% , 53.3% and 26.7% in group I , II and III respectively .These 3 symptoms were the most common presenting symptoms.

In agreement with our study, **Mao et al. [15]** showed that fever (73%), cough (69%), and fatigue (40%) were the most prevalent symptoms at disease onset in patients recovered from COVID-19. There was a statistically non-significant difference between moderate and severe / critically ill patients in their study (P=0.98 , 0.741 and 0.725 respectively)

In addition, **Ganet al. [16]**showed that the most common symptoms were fever (97.5%) followed by fatigue (45.6%), cough (41.8%), and chest distress (32.9%).

However **,Bertin et al. [17]** found that the most prevelantmanifistations are persistent fatigue, dyspnea, anosmia and memory disturbance . Differences between these results and our results may be attributed to different range of participants age or their health conditions.
In this study we found that there is statistically non-significant difference between the studied groups regarding COVID severity which was detected by measured O2 saturation and CT findings during infection . The mean O2 saturation level was 82.4, 89.8 and 90.2 in group I , II and III with 33.3% , 20% and 13.3 % positive CT findings among the three studied groups respectively .
Our results agree with study of**Yan et al. [18]** who demonstrated that oxygen saturation ratio measured by pulse oximetry is a simple indicator which has been previously used in the cases of acute respiratory distress syndrome instead of other complex variables, and so it can be measured in each patient with COVID-19 pneumonia to help identify high risk patients .
In attemptto predict COVID-19 disease severity **Shiri et al. [19]** constructed a model based on CT radiomics. Another study aimed to evaluate some radiomics features to assess patients' severity by **Yip et al. [20]** in which the patients were classified into three categoriesbased on severity into mild, moderate, and severe.

We demonstrated that there is no statistically significant difference between the studied groups as regard to hemoglobin and platelet count. While there is statistically significant difference between the studied groups regarding white blood cell count. On doing post-hoc LSD comparison, the difference is significant between group I (patients recovered from COVID-19 from 1-3 months) and control group. There is statistically significant increase in neutrophil count .Also our results demonstrated statistically significant decrease in lymphocytic count with increased Neutrophil / Lymphocyte ratio (NLR) in group I as compared to other studied groups
This agree with **Chowdhury et al. [21]** who found that a significant difference was found in a t-test among initial hematological parameters during admission with 4 weeks post COVID-19 follow up (P=0.36). However, they hadn´t found any significant differences in RBC, platelet, and hemoglobin levels ($p > 0.05$).
Moreover, **Gameil et al. [13]** study revealed that there was a significant differences in WBCs count and platelet count among cases in comparison with control group .Also , in logistic regression in prediction of COVID-19 survivors done in **Gameil et al. [13]** study , WBCs count,Hb concentration and Platelet count were statistically significant independent predictors in univariate analysis .
In this study as regard to kidney function testresults , there wasn´t a significant difference between patients groups and control group as regard urea . however serum creatinine hasstatistically significanthigher levels in early follow up patients group.This come in agreement with **Gameil et al. [13]** study whereserum BUN,creatinine, and urine albumin /creatinineratio show significant elevation whileeGFR was relatively reduced in COVID-19 survivors than other subjects with no history of COVID-19. Also **Hong et al. [22]** results show significant elevation in serum BUN, creatinine, together with micro-albuminuria during COVID-19 disease then partially improveafter recovery over a period of more than one month.
During acute COVID-19 disease Pattern of liver damagehad been identified enormously, however, the long-term sequale of COVID-19 live functions is still unclear **An W et al.[23] .**In the current study, there is statistically significant increase in the studied groups regarding total protein , where it had lower levels in patients groups than control group . ALT and AST had higher levels in patients group I than the other studied groups. There is statistically non-significant difference between the studied groups regarding albumin, direct or total bilirubin.

In agreement with our result**Gameil et al. [13]** found no significant difference between patients recovered from COVID-19 and healthy control subjects regarding serum bilirubin.However serum albumin was significantly reduced among their COVID-19 survivors. Moreover; they showed significant higher level of ALT, AST, GGT, and ALP among COVID-19 survivor, which coincide with this study results.
Also our results run with **Ya Wen et al.[24]**study in which higher levels of ALT, GGT and ALP along with lower level of serum albumin were encountered in recovered COVID-19 patients during the 14 days after discharge whichgradually return to normal within period of two months.

Liver aminotransferases were also elevated to mild or moderate degree among COVID-19 patientsin the study conducted by**Fan et al. [25]** then return to normal and not associated with increases total bilirubinin serum. The same result was reached also by**Xu et al. [26]** who reported no elevation of bilirubin in serum.
The differences in liver and kidney functions between our study and the previous studies may be due to different degree of severity with different time of follow up.
In this study there wasn´t a statistically significant difference between the three COVID-19 recovered groups and control group as regard serum Calcium level .However, patients groups had significantly lower Magnesium and Phosphorus levels than control group. This can be attributed to several factors such as inadequate fluid intake due to illness, starvation, muscle weakness, respiratory hypoxia / failure or shift from extracellular space to intracellular space.
This runs with **Gameil et al. [13]** who found no statistically significant difference as regard Ca. However; a statistically significant higher level of Mg was encounteredamong their 120 COVID-19 survivors than healthy participants.
Our study showed statistically significant differences in Na level between each group and control group. It had lower level in early follow up than control group. This can be attributed to hypovolemia, vomiting, SIADH fever or diarrhea **[27].**
Moreover; we found a statistically significant lower k level in early follow up patients. This runs in agreement with **Alfano et al. [28]** who detected lower K level in 41% of patients during hospitalization. This can be attributed to fever,hyperventilation,medications, sweating and dietary changes.

However,**Gameil et al.[13]**showed that there wasn´t a statistically significant difference between COVID-19 survivorsand healthy participants as regard Na and K levels.
As regard to coagulation profile we demonstrated that there is statistically non-significant difference between the studied groups regarding APTT, PT, INR or fibrinogen**.** On the other hand, there is a significant higher D-dimer level in early follow up patients group I.
Our results agree with, **Townsend et al. [29]** whofound that PT and APTT had normalized in more than 90% of adult patients duringconvalescence.

Chowdhury et al.[30]observed high PT at initial admission days in 22.6 % of cases and in 4 weeks post recovery follow up which coincide with our results where PT level is slightly higher in early recovered patients than others.
In the present study, there is statistically significant difference between the studied groups regarding IgA being higher among recovered patients than healthy subjects. On doing pairwise comparison, the difference is significant between group (III& II), (III &control group) and also between (control group & and I). There is statistically non-significant difference between the studied groups regarding RF, C4, C3, IgG or IgM though IgG and IgM had higher levels in recovered patients than non-COVID19 subjects. There is statistically significant difference between the studied groups regarding CRP being higher in all patients groups than control group on doing pairwise comparison. There is statistically non-significant difference between the studied groups regarding ESR or LDH.
In agreement with our study,**Ivanovet al. [31]** found high levels of IgA antibodies which persist beyond six months after COVID-19 recovery.Alsoaverage level of IgG increased after 1 month of diagnosis then gradual decreases in Ab level through observation period.
In addition, our results run with **MohiuddinChowdhury et al. [21]** who found a significant difference among initial CRP during admission with the post-COVID-19 follow-ups. Also**, Sandra et al. [32]** and **Mandal et al. [33]** found that inflammatory markers specially CRP were persistently elevated in meta-analysis study, similar result was reached by**Gameilet al. [13]**.
In this study there is a significant increase in ferritin level in early follow up patients group I than in control group. Our results agree with **Gameilet al. [13]** who found significantly higher ferritin level among COVID-19 survivors than healthy control and showed significant differences in the inflammatory markersbetween the

studied groups denoting persistent long term inflammatory process residue. In addition, **Bertin et al. [17]** showed persistent inflammatory biological syndrome.

In contrast to our study; **Gameil et al.[13]**found a significantly higher ESR among COVID-19 survivor than healthy subjects. This discrepancy in results can be attributed to early assessment of cases and their lost during follow up.

This study demonstrated that four patients (26.7%) within group I, two patients (13.3%) within group II and two patients (13.3%) within group III of COV ID-19 survivor had positive value of Antiphospholipid antibodies without statistically significant difference eitherin between patients groups or between patients and control groups.

In agreement with our study, there were studies that found few positive Antiphospholipid antibodies test results among their studied patient cohorts and showed the critical pathogenic role of Antiphospholipid antibodies in COVID-19 in which antibodies were measured and then correlated to occurrence of thrombosis **[34].**

Positive results of antiphospholipid antibodies in acute COVID-19 had been reached by several research groups. Infections are found to induce transient production of APL, this phenomenon led to the necessity for persistent positive APL results for at least 12 weeks before diagnosis ofantiphospholipid syndrome[**35].**

Taha et al. [36] found persistent Antiphospholipid antibodies positivity for one year following COVID-19 acute infection and demonstrated as independent factors related to disease severity, so it can be biological predictors of post-COVID syndrome.

Positive Antiphospholipid antibodies has been found in 13.9% of COVID-19 patientsand in more than 50% of patients encontered severe COVID-19, whereas in general population the prevalence of Antiphospholipid antibodies was only 1.5% **[37].**

The prevalence of Antiphospholipid antibodies in post-COVID syndrome patients and its pathophysiological mechanism remain undefined, however some hypotheses have been suggested such as; viral persistence particularly in nervous system, autoimmune or inflammatory reaction that occur following infection, or involvement of microglia**[38].** Antiphospholipid antibodies may accompany viral infections and could have pro-inflammatory effects which may be persistent in this context**[39].**

5.0 Conclusion:

Several hematological and immunological parameters may remain affected even after recovery from COVID-19 and the degree of impact on these parameters can be related to the severity of the disease and to the health condition of the patient. Laboratory parameters helped us to understand the pathology of the disease and hence may assist in controlling it properly;also these parameters can be used as prognostic indicators for the disease.

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