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Effect of Coronavirus Infection on Haematological Parameters in Covid-19 Patients in the Sabratha Region Western Libya

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Abstract

***Background:** The coronavirus disease 2019 (COVID-19) is an aggressive virus that spread worldwide and caused a pandemic infection. It is a systemic disease involving multiple systems, including respiratory, cardiovascular, gastrointestinal, hematopoietic, neurological, and immune systems. White blood cells, hemoglobin, and platelets have a role in the development of signs and symptoms of coronavirus disease 2019.*

***Objectives:** The present study aimed to investigate the haematological changes during Corona Virus infection among COVID-19 patients in the Sabratha region, Western Libya.*

***Subjects and Methods:** Thirty Confirmed COVID-19 patients hospitalized in the Isolation Centre located in Sabratha city, Libya from the 2nd October, 2020 to the 15th March, 2021, were enrolled in this prospective study. Covid-19 patients were defined as positive cases after the detection of SARS-CoV-2 RNA in oro-nasopharyngeal swab samples. Data collected included demographic, clinical, and biological factors. Also, 30 healthy individuals without any chronic disease or respiratory symptoms were recruited for the control group. Blood samples were collected by vein puncture 5 ml of venous blood withdrawn from each participant in the study by using disposable syringes under an aseptic technique; they then transferred to a sterile EDTA tube, for complete blood count. Haematological parameters were determined using an automated haematology analyzer Sysmex (KX 21) machine in the Sabratha Isolation Centre laboratory. The statistical significance of differences between groups was evaluated with the Kruskal-Wallis H test. Correlations between the age and haematological parameters were evaluated with the Spearman's test.*

***Results:** The results showed that coronavirus infection caused a significant (P=0.0088) decrease in hemoglobin concentration, MCH (P=0.0008), MCHC (P< 0.0001), lymphocytes % (P< 0.0001), and mixed % (P=0.2496), and a significant increase in RDW-SD (P=0.0064), RDW-CV (P=0.0005), leukocytes count (P<0.0001), neutrophils % (P<0.0001), and neutrophils/lymphocytes ratio (P< 0.0001), and Platelets/Lymphocytes ratio (P< 0.0001) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals. The percentages of corona virus-infected patients with leukopenia were 3.3% at 0 day and 14 days of hospital admission, anemia was 26.7%, 16.7%, and 33.3%, leukocytosis was 60%, 56.7, and 50%, lymphocytopenia was 63.3%, 56.7%, and 43.3% and neutrophilia was 76.7%, 76.7%, and 60%, and with thrombocytopenia was 13.3%, 16.7%, and 10% at 0 day, 14 days, and 21 days of hospital admission, respectively. There were recorded a significant positive correlation between age of patients and WBCs count, Hb, Hct, MCV, RDW-SD, RDW-CV, PDW, and P-LCR, and a significant negative correlation with MXD%. Also, results showed that a significant positive correlation between WBCs count and Neutrophils %, RBCs count, Hb, Hct, RDW-SD, RDW-CV, PDW, and P-LCR, and a significant negative correlation with MXD%, Platelets count, and PCT. In addition, there was a significant positive correlation between lymphocytes % and MXD% and a significant negative correlation with Neutrophils %. There was a significant negative correlation between Neutrophils % and Lymphocytes % and MXD%. There was a significant negative correlation between MXD% and RBCs count, Hb, Hct, RDW-SD, RDW-CV, and PDW.*

Conclusion: *It can be concluded that coronavirus infection caused a significant decrease in hemoglobin, MCH, MCHC, lymphocytes %, mixed %, and a significant increase in RDW-SD, RDW-CV, leukocyte count, neutrophils %, and neutrophils/lymphocytes ratio in patients compared to the controls. There was a significant correlation between age, WBCs count, lymphocytes %, neutrophils %, MXD%, and some haematological parameters. The effects of coronavirus infection on hematological alterations are still poorly understood so, further haematological studies are needed to confirm these results. These haematological changes may help the clinicians to better understand the COVID-19 and provide more clinical treatment options.*

Keywords: *SARS-CoV-2, COVID-19, Coronavirus, Leukocytosis, Lymphocytopenia, Neutrophilia,Thrombocytopenia, Hematological parameters, Sabratha region, Western Libya.*

Abbreviations

ACE2 receptor: Angiotensin-converting enzyme 2 receptor; ALC: Absolute Lymphocyte Count; AUC: area under the curve; CBC: complete blood count; CI: Confidence Interval; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; GSCF: Granulocyte colony-stimulating factor; ICU: Intensive care unit; IFCC: International Federation of Clinical Chemistry; IL-6: Interleukin 6; IP10: interferon-inducible protein-10; IQR: interquartile range; LDH: lactate dehydrogenase; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCP-1: Macrophage Inflammatory Protein-1; MERS: Middle East respiratory syndrome; MIP1: Macrophage inflammatory protein 1; MPV: mean platelet volume; MSCs: mesenchymal stem cells; NCID: national center for infectious diseases; NLR: neutrophil-to-lymphocyte ratio; Neut/Lymph: Neutrophils/Lymphocytes Ratio; PCT: the volume occupied by platelets; PDW: platelet distribution width; P-LCR: platelet large cell ratio; PLR: platelet-to-lymphocyte ratio; PLTs/Lymph: platelets/lymphocytes ratio; PT: prothrombin time; PTT: partial thromboplastin time; RBCs: red blood corpuscles; RDW-CV: cell distribution width (RDW-CV); RDW-SD: cell distribution width (RDW-SD); RNA: ribonucleic acid; SARS: severe acute respiratory syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TNF: Tumor necrosis factor.

Introduction

Coronavirus disease 2019 is caused by the severe acute respiratory syndrome coronavirus 2. It belongs to the family Coronaviridae, with 80% genomic similarities to Severe acute respiratory syndrome coronavirus. It is affecting more than 100 million of patients worldwide. [1].

Coronaviruses are known to cause colds and other severe diseases, like SARS and Middle Eastern Respiratory Syndrome [2, 3]. The coronavirus disease 2019 is an aggressive virus spread worldwide and caused pandemic infection and there is an urgent need to identify a predictor whether clinical or laboratory [3, 4]. It is a systemic disease involving multiple systems, including respiratory, cardiovascular, gastrointestinal, hematopoietic, neurological, and immune systems [5-8].

Adverse outcomes of COVID-19 were associated with comorbidities, including cardiovascular disease, lung disease, and hypertension. These conditions are more prevalent in men and linked to smoking and drinking alcohol [9, 10]. Epidemiological studies showed that elder patients were more susceptible to severe diseases [10, 11], while children tend to have milder symptoms [10, 12, 13].

COVID-19 is from the same group of ribonucleic acid (RNA) viruses that caused severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [14-17]. Coronaviruses are enveloped, none segmented, single-stranded, positive-sense RNA viruses named after their corona- or crown-like surface projections observed on electron microscopy that correspond to large surface spike proteins. Coronaviruses are classified in the Nidovirales order [17-19].

Now the challenged against COVID-19, not only to the diagnosed virus but to predict the progression towards severe and fatal forms, these predictors will enable risk stratification, guide interventional studies to target patients at enhanced risk of developing severe disease and optimize the allocation of limited human and technical resources in the ongoing pandemic. Moreover, identification of laboratory

parameters capable of discriminating between severe and non-severe cases, or those at high or low risk of mortality, will allow for improved clinical situational awareness [3]. White blood cells, hemoglobin, and platelets have a role in the development of signs and symptoms of coronavirus disease 2019 [4]. During the incubation period of COVID-19, usually ranging from 1 to 14 days, and during the early phase of the disease, when non-specific symptoms are present, peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced [8]. The non-alteration of the erythroid lineage, such as hemoconcentration and a slight numerical alteration of platelets, when present, also contrasts with severe dengue [20, 21]. Various hematological parameters alteration has been documented in the Chinese literature in SARS-Cov-2 infection [22]. Lymphopenia was commonly seen in coronavirus-infected patients and correlates with disease severity [1].

Objectives

The present study aimed to investigate the haematological changes during Corona Virus infection among COVID-19 patients in the Sabratha region, Western Libya

Subjects and Methods

Thirty Confirmed COVID-19 patients hospitalized in the Isolation Centre located in Sabratha city, Libya from the 2nd October 2020 to the 15th March 2021, were enrolled in this prospective study. Covid-19 patients were defined as positive cases after the detection of SARS-CoV-2 RNA in oro-nasopharyngeal swab samples. This study was approved by the Research and Ethical Committee of the Faculty of Medicine, Sabratha University. Demographic data were extracted from electronic medical records and patient files. Data collected included demographic, clinical, and biological factors, as well as complications at admission and during the hospital stay. Any missing or uncertain data were collected and clarified through direct communication with the relevant health care providers and family members of patients. Also, 30 healthy individuals without any chronic disease or respiratory symptoms were recruited for the control group. Blood samples were collected by vein puncture 5 ml of venous blood withdrawn from each participant in the study by using disposable syringes under an aseptic technique; they then transferred to a sterile EDTA tube, for complete blood count.

Determination of Haematological Parameters

Red blood cells count, haemoglobin concentration, hematocrit value, Mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, cell distribution width RDW-CV, RDW-SD, white blood cells (WBCs) count, differential count of leucocytes, and blood platelets count and their indices were determined using an automated haematology analyzer Sysmex (KX 21) machine in the Sabratha Isolation Centre laboratory.

Statistical Analysis

Continuous variables were presented as medians (interquartile range [IQR]); categorical variables were presented as counts (%). The data were analyzed using Graph Pad Prism software version 7. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. The statistical significance of differences between groups was evaluated with the Kruskal-Wallis H **test**. Correlations between the age and haematological parameters were evaluated with the **Spearman's** test. A *P*-value of *<0.05* was used to establish statistical significance.

Results

The mean age of the patients was 64 years (30–90 years); thirty patients, 18 males (63.3%) and 11 females (36.7%) were included in the current study (Figure. 1).

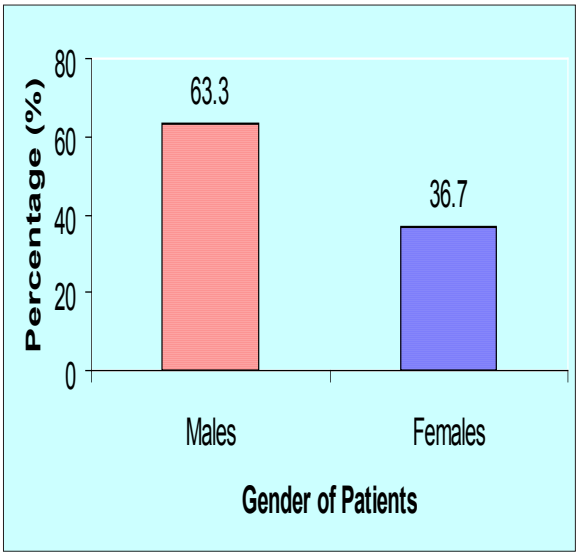

Fig1. *Distribution of patients according to gender.*

Effect of Coronavirus Infection on RBCs Count and its Indices in Covid-19 Patients

The results in table.1 and figure (3) show that patients with COVID-19 had a significant (P=0.0088) decrease in hemoglobin concentration [(median (IQR) g/dl], 13.35 (11.73-14.00), 13.05 (12.10-14.05), and 12.60 (11.45-13.60) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (13.95 (12.70-15.53). Also, MCH (Pg) and MCHC (g/dl) [median (IQR)] were significantly decrease in patients at 0 day, 14 days, and 21 days [28.00 (26.00-29.00), 27.75 (26.50-29.25), and 27.85 (26.45-29.00) compared with the controls 29.00 (28.23-31.00); P=0.0008 and 33.00 (32.00-33.93), 33.00 (32.30-33.20), and 33.00 (32.00-33.93), compared with the controls 35.00 (33.78-36.25) ; P< 0.0001, respectively (Table. 1& Figures . 6, 7).

On the other hand, Coronavirus infection caused a significant increase in RDW-SD and RDW-CV [median (IQR)], 39.15 (37.35-44.38), 42.60 (37.93-47.03), and 41.70 (38.33-46.50 compared with the controls 38.20 (37.50-39.70); P=0.0064, and 13.10 (12.38-14.40), 13.25 (12.20-14.68), and 13.30 (12.58-14.80) compared with the controls12.10 (11.90-13.13); P= 0.0005, respectively (Table. 1& Figures. 8, 9).

RBCs count, Hct value, and MCV show a none significant changes in coronavirus infected patients compared to the controls (P=0.9009, P=0.6678, and P= 0.9630, respectively) (Table.1 & Figures . 2, 4& 5)

Table1. *Median (IQR) of erythrocytes count and its indices in control and during COVID-19 Virus infection among COVID-19 Patients.*

Groups Parameters	Control Median (IQR)	0 day Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	Kruskal-Wallis Statistic	P Value (Summary)
RBCs count ($x\ 10^6/\mu L$)	4.78 (4.30-5.15)	4.72 (4.36-4.95)	4.64 (4.31-5.04)	4.72 (4.30-4.89)	0.5805	0.9009 (ns)
Hemoglobin (g/dl)	13.95 (12.70-15.53)	13.35 (11.73-14.00)	13.05 (12.10-14.05)	12.60 (11.45-13.60)	11.61	0.0088 (**)
Hct (%)	38.95 (35.28-42.95)	38.95 (33.90-42.50)	40.15 (37.28-42.50)	38.55 (33.78-41.78)	1.563	0.6678 (ns)
MCV (μ^3)	83.05 (80.40-88.03)	83.95 (79.60-87.50)	84.00 (79.95-89.25)	84.00 (79.08-89.00)	0.2839	0.9630 (ns)
MCH (Pg)	29.00 (28.23-31.00)	28.00 (26.00-29.00)	27.75 (26.50-29.25)	27.85 (26.45-29.00)	16.81	0.0008 (***)
MCHC (g/dl)	35.00 (33.78-36.25)	33.00 (32.00-33.93)	33.00 (32.30-33.20)	33.00 (32.00-33.93)	22.21	< 0.0001 (***)
RDW-SD	38.20 (37.50-39.70)	39.15 (37.35-44.38)	42.60 (37.93-47.03)	41.70 (38.33-46.50)	12.31	0.0064 (**)
RDW-CV	12.10 (11.90-13.13)	13.10 (12.38-14.40)	13.25 (12.20-14.68)	13.30 (12.58-14.80)	17.71	0.0005 (***)

IQR: Interquartile range, ns: none significant difference compared with the controls , (**) significant difference compared with the controls at (P<0.01), (***) significant difference compared with the controls at (P<0.001).

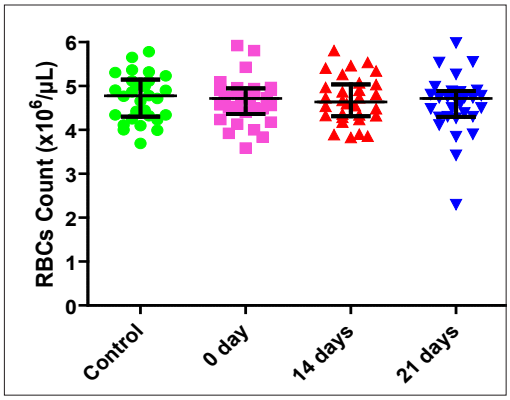

Fig2. *Median (IQR) of RBCs count in controls and during COVID-19 Virus Infection among COVID-19 Patients.*

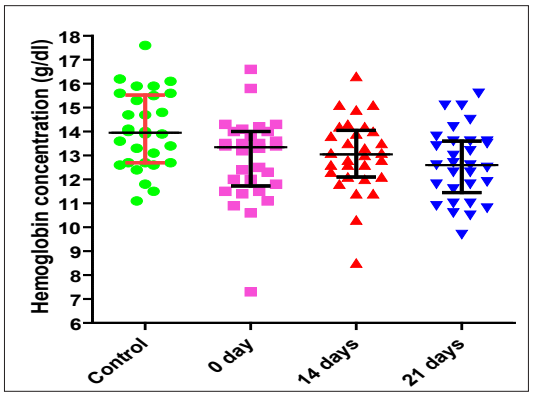

Fig3. *Median (IQR) of hemoglobin concentration in controls andduring COVID-19 Virus Infection amongCOVID-19 Patients.*

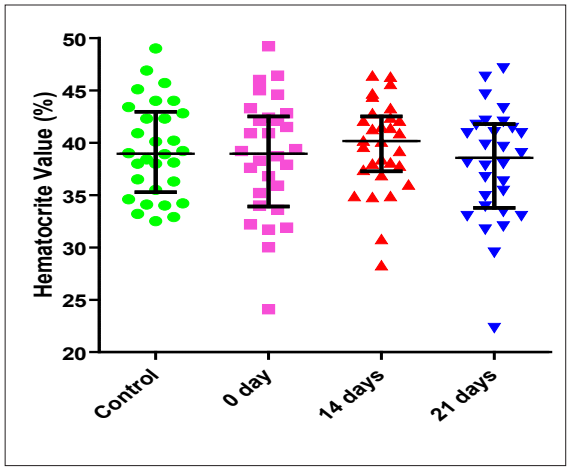

Fig4. *Median (IQR) of hematocrit value in controls and during COVID-19 Virus Infection among COVID-19 Patients.*

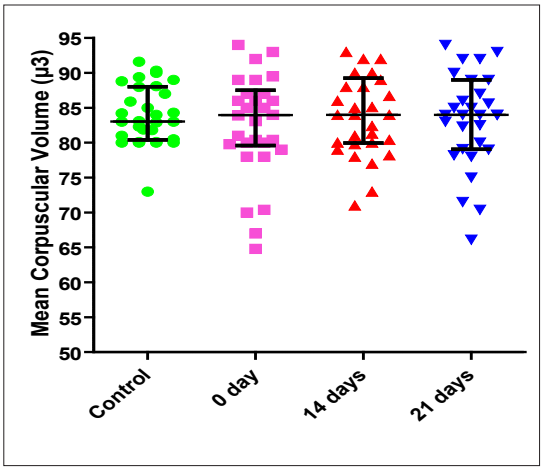

Fig5. *Median (IQR) of mean corpuscular volume in controls and during COVID-19 Virus Infection among COVID-19 Patient*

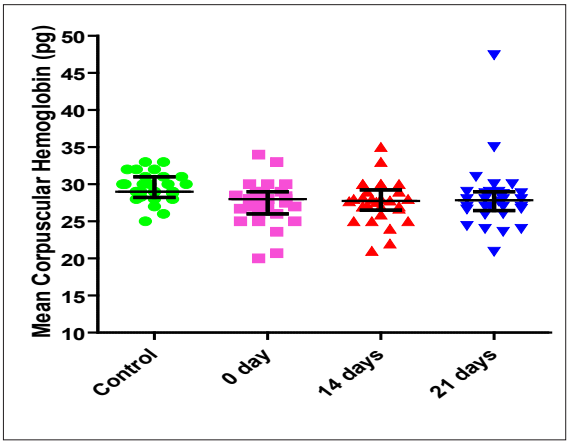

Fig6. *Median (IQR) of mean corpuscular hemoglobin in controls and during COVID-19 Virus Infection among COVID-19 Patients.*

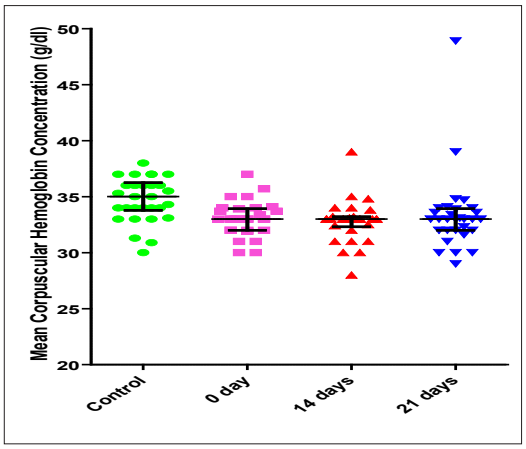

Fig7. *Median (IQR) of mean corpuscular hemoglobin concentration in controls and during COVID-19 Virus Infection among COVID-19 Patients.*

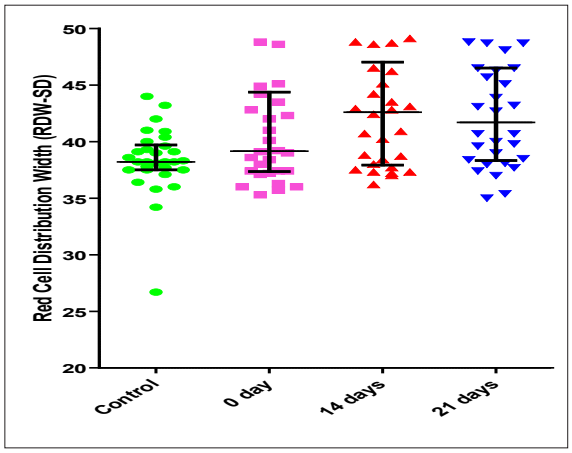

Fig8. *Median (IQR) of red cell distribution width (RDW-SD) in controls and during COVID-19 Virus Infection among COVID-19 Patient*

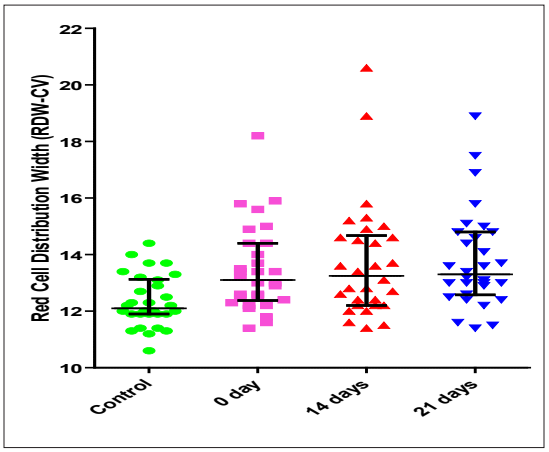

Fig9. *Median (IQR) of cell distribution width (RDW-CV) in controls and during COVID-19 Virus Infection among COVID-19 Patient*

The percentage of coronavirus-infected patients with anemia (Hb<12) was 26.7%, 16.7%, and 33.3% at 0 day, 14 days, and 21 days of hospital admission (Table. 2 % Figure. 10).

Table2. *Frequency and percentage of coronavirus infected patients for hemoglobin concentration less than 12 and more than or equal 12 g/dl at different periods of infection.*

Parameter	Groups	0 day Frequency (%)	14 days Frequency (%)	21 days Frequency (%)
Hemoglobin Concentration (g/dl)	<12	8 (26.7)	5 (16.7)	10 (33.3)
	≥12	22 (73.3)	25 (83.3)	20 (66.7)

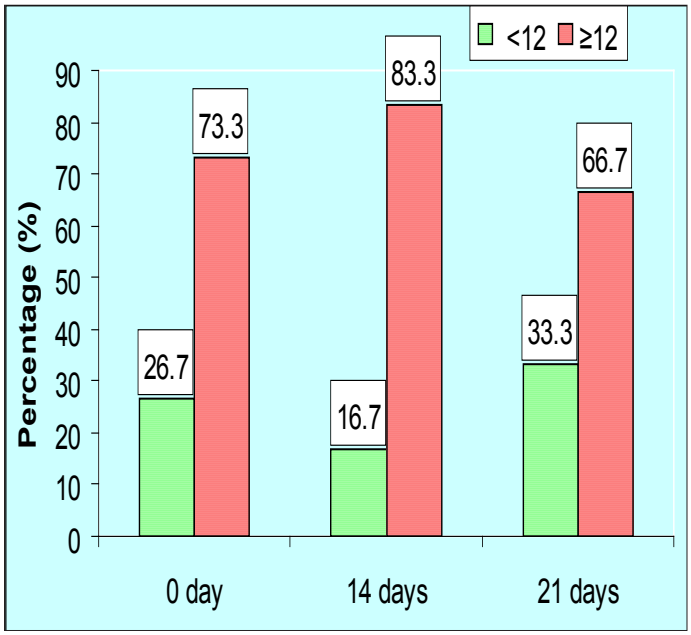

Fig10. *Percentage of coronavirus infected patients with hemoglobin concentration <12 and ≥12 g/dl at different periods of infection*

Effect of Coronavirus Infection on Leukocytes Count and Differential Count of Leukocytes in Covid-19 Patients

The results in a table.3 show that patients with COVID-19 had a significant (P< 0.0001) increase in leukocytes count [(median (IQR) x 10^3/µL], 12.95 (7.80-17.45), 12.25 (780-15.23), and 9.75 (7.40-14.52) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (7.20 (5.30-8.93) (Figures . 11), neutrophils % [(median (IQR) %], 84.00 (72.48-89.00), 79.00 (64.83-91.25), and 67.60 (60.75-89.25) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (67.60 (60.75-89.25)) (Figures .13), and Neutrophils/Lymphocytes ratio [(median (IQR) %], 10.34 (4.41-12.71), 8.19 (2.41-22.75), and 5.06 (2.15-15.95) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (1.63 (1.18-2.12)) (Figures . 15). On the other hand, data in table. 3 and figure.12&13 show that a significant (P< 0.0001) decrease in lymphocytes % [(median (IQR) %], 14.00 (7.00-19.00), 12.00 (4.50-26.40), and 23.00 (5.75-29.00) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (35.10 (29.73-41.25)), and at P=0.2496 in mixed % [(median (IQR) %], 6.60 (4.25-10.00), 5.70 (3.80-10.43), and 8.45 (5.53-11.33) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (8.75 (4.98-11.78)).

Table 3. *Median (IQR) of Leukocytes count and differential count of leukocytes in control and during COVID-19 Virus Infection among COVID-19 Patients*

Groups Parameters	Control Median (IQR)	0 day Median (IQR)	14 days Median (IQR)	21 days Median (IQR)	Kruskal-Wallis Statistic	P Value (Summary)
WBCs count (x 10^3/µL)	7.20 (5.30-8.93)	12.95 (7.80-17.45)	12.25 (780-15.23)	9.75 (7.40-14.52)	26.34	< 0.0001 (***)
Lymphocytes %	35.10 (29.73-41.25)	14.00 (7.00-19.00)	12.00 (4.50-26.40)	23.00 (5.75-29.00)	41.29	< 0.0001 (***)
Neutrophils %	56.95 (50.00-65.10)	84.00 (72.48-89.00)	79.00 (64.83-91.25)	67.60 (60.75-89.25)	32.20	< 0.0001 (***)
Mixed %	8.75 (4.98-11.78)	6.60 (4.25-10.00)	5.70 (3.80-10.43)	8.45 (5.53-11.33)	4.112	0.2496 (ns)
Neut/Lymph Ratio	1.63 (1.18-2.12)	10.34 (4.41-12.71)	8.19 (2.41-22.75)	5.06 (2.15-15.95)	37.96	< 0.0001 (***)

IQR: Interquartile range, ns: none significant difference compared with the controls , (***) significant difference compared with the controls at (P<0.001).

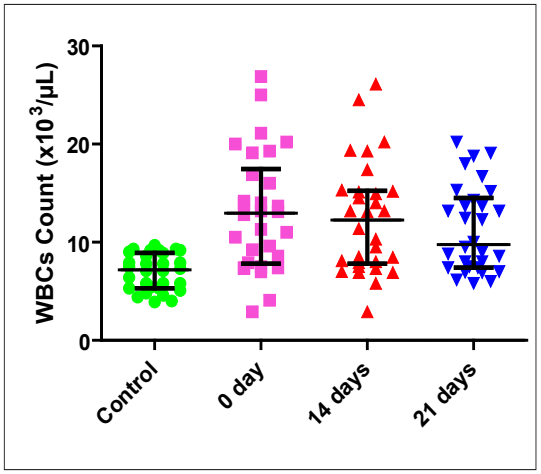

Fig11. *Median (IQR) of WBCs count in controls and during COVID-19 Virus Infection among COVID-19 Patients*

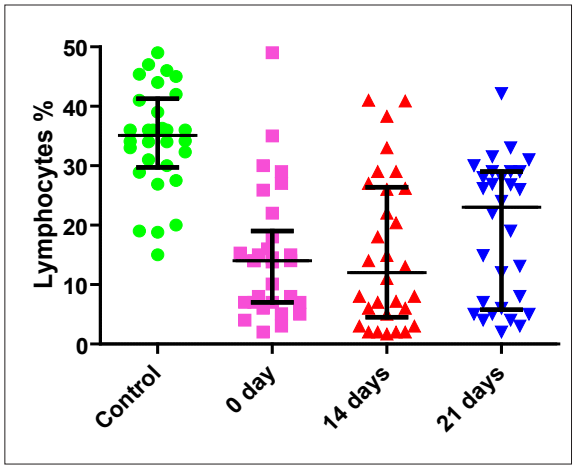

Fig12. *Median (IQR) of Lymphocytes % in controls and during COVID-19 Virus Infection among COVID-19 Patient.*

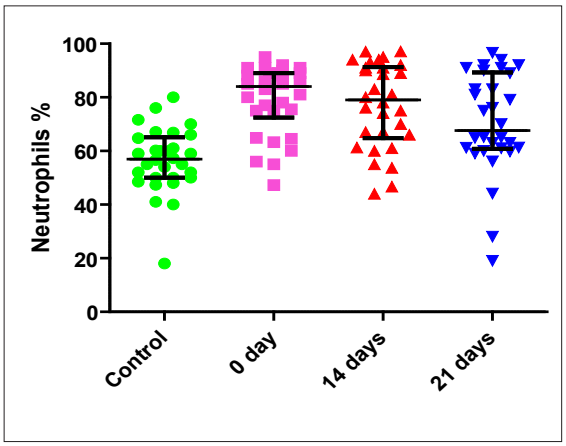

Fig13. *Median (IQR) of Neutrophils % in controls and during COVID-19 Virus Infection among COVID-19 Patient*

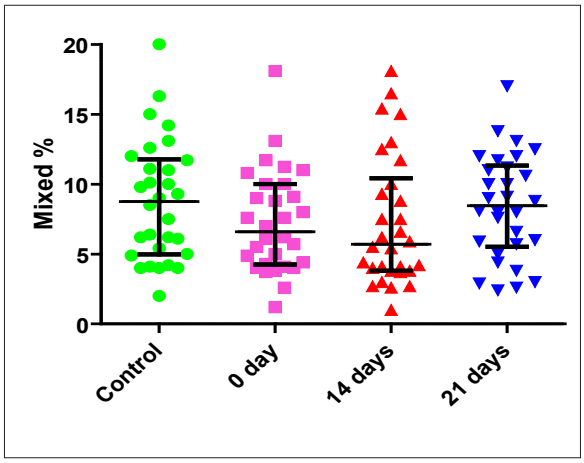

Fig14. *Median (IQR) of Mixed % in controls and during COVID-19 Virus Infection among COVID-19 Patient*

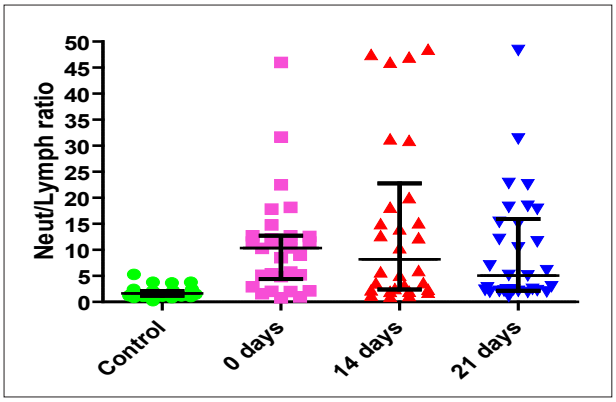

Fig15. *Median (IQR) of Neutrophils/Lymphocytes Ratio in controls and during COVID-19 Virus Infection among COVID-19 Patient*

The percentages of corona virus infected patients with leukopenia (WBCs count <4 x 10^3/µL) were 3.3% at 0 day and 14 days of hospital admission, respectively, (4-10) x 10^3/µL was 36.7%, 40%, and 50% at 0 day, 14 days, and 21 days of hospital admission, respectively, and patients with leukocytosis (>10 x 10^3/µL) was 60%, 56.7, and 50% at 0 day, 14 days, and 21 days of hospital admission, respectively (Table. 4 % Figure. 16).

The percentages of lymphocytopenia in corona virus infected patients (<20 %) were 63.3%, 56.7%, and 43.3% at 0 day, 14 days, and 21 days of hospital admission, respectively (Table. 4 % Figure. 17). The percentages of corona virus infected patients with neutrophilia (>65 %) was 76.7% at 0 day and 14 days, and 60% at 21 days of hospital admission (Table. 4 % Figure. 18).

Table4. *Frequency and percentage of coronavirus infected patients for WBCs count, Lymphocytes %, and Neutrophils % at different periods of infection.*

Parameters	Groups	**0 day** Frequency (%)	**14 days** Frequency (%)	**21 days** Frequency (%)
WBCs count (x 10^3/µL)	<4 x 103/µL	1 (3.3)	1 (3.3)	-
	(4-10) x 103/µL	11 (36.7)	12 (40)	15 (50)
	>10 x 103/µL	18 (60)	17 (56.7)	15 (50)
Lymphocytes %	<20 %	19 (63.3)	17 (56.7)	13 (43.3)
	≥20 %	11 (36.7)	13 (43.3)	17 (56.7)
Neutrophils %	≤65%	7 (23.3)	7 (23.3)	12 (40)
	>65 %	23 (76.7)	23 (76.7)	18 (60)

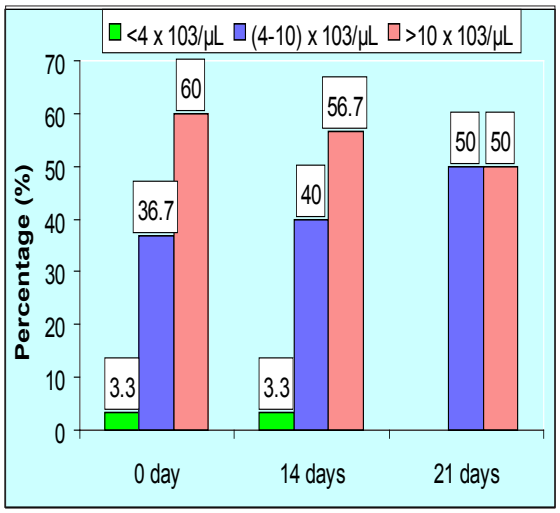

Fig16. *Percentage of coronavirus infected patients in WBCs count [<4, (4-10), & >10) x 103/µL] at different periods of infection*

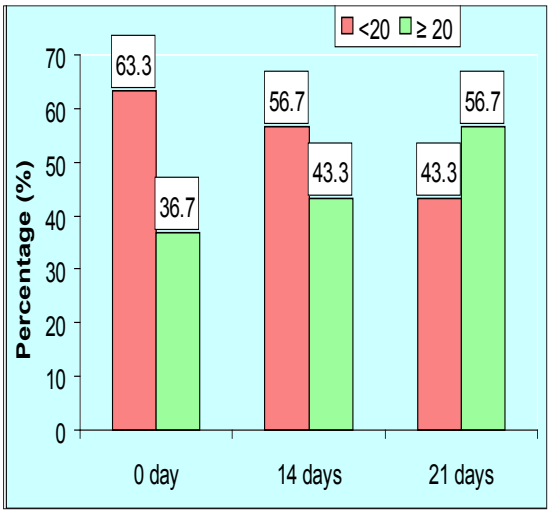

Fig17. *Percentage of coronavirus infected patients in <20%& ≥20% lymphocytes % at different periods of infection*

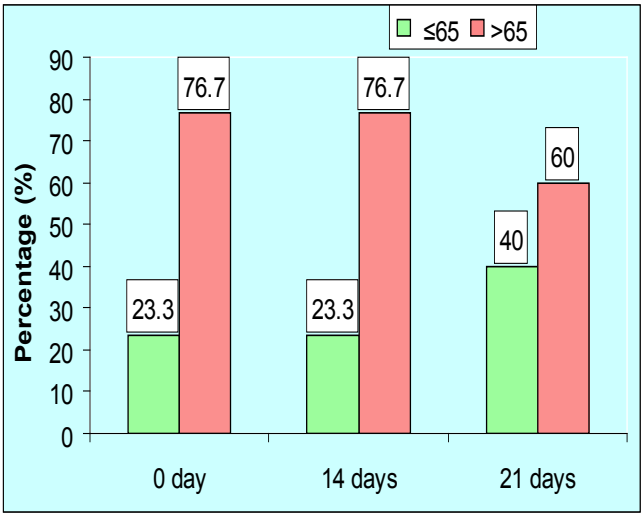

Fig18. *Percentage of coronavirus infected patients in ≤65%& >65% Neutrophils % at different periods of infection*

Effect of Coronavirus Infection on Platelets Count and its Indices in Covid-19 Patients

Platelets count, PDW, MPV, P-LCR, and PCT show a none significant changes (P=0.7761, P=0.5323, P= 0.7475, P= 0.9757, and P= 0.1205, respectively) in coronavirus infected patients compared to the controls (Table.5 & Figures. 19-23).

Platelets/Lymphocytes ratio show a significant increase (P< 0.0001), 231.5 (135.8-313.5), 236 (138.0-338.3), and 180.5 (128.0-290.8) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (114.5 (94.00-129.8) (Table.5 & Figures . 24).

Table5. *Median (IQR) of platelets count and its indices during COVID-19 Virus Infection among COVID-19 Patients.*

Groups Parameters	**Control** Median (IQR)	**0 day** Median (IQR)	**14 days** Median (IQR)	**21 days** Median (IQR)	**Kruskal-Wallis Statistic**	**P Value (Summary)**
Platelets Count (x10³/µL)	259 (200-299)	263 (207-302)	285 (176-374)	258 (202-319)	1.104	0.7761 (ns)
PDW (%)	12.25 (10.63-13)	11.85 (10.58-13.53)	12.55 (10.45-13.60)	11.10 (9.78-13.73)	2.198	0.5323 (ns)
MPV (fL)	9.85 (8.98-10.20)	9.85 (8.70-10.60)	9.85 (9.78-10.73)	9.80 (8.55-10.60)	1.223	0.7475 (ns)
P-LCR	24.05 (19.60-27.93)	24.80 (16.80-30.60)	25.10 (13.15-30.83)	24.40 (15.53-30.13)	0.2116	0.9757 (ns)
PCT	0.220 (0.198-0.270)	0.265 (0.23-0.33)	0.295 (0.20-0.35)	0.260 (0.20-0.350)	5.825	0.1205 (ns)
PLTs/Lymph ratio	114.5 (94.00-129.8)	231.5 (135.8-313.5)	236 (138.0-338.3)	180.5 (128.0-290.8)	23.72	< 0.0001 (***)

IQR: Interquartile range, ns: none significant difference compared with the controls , (***) significant difference compared with the controls at (P<0.001).

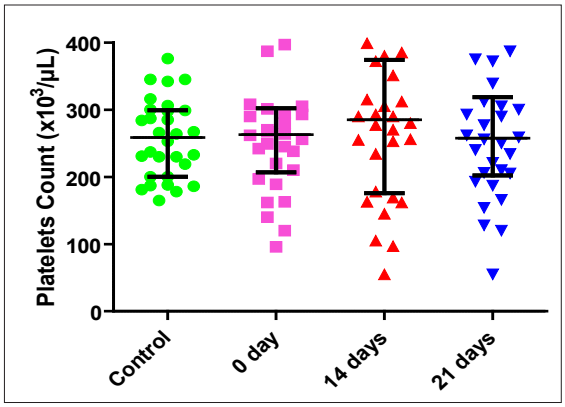

Fig19. *Median (IQR) of platelets count in control and during COVID-19 Virus Infection among COVID-19 Patients*

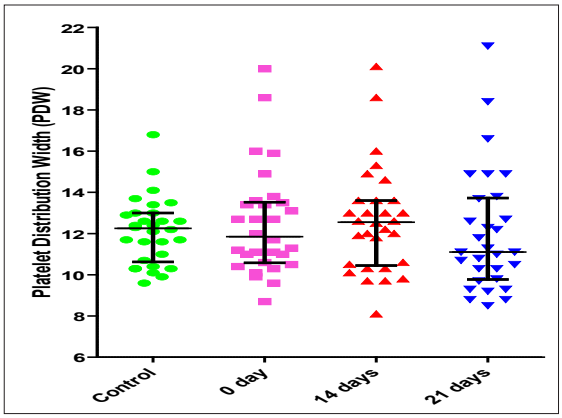

Fig20. *Median (IQR) of platelet distribution width (PDW) in control and during COVID-19 Virus Infection among COVID-19 Patients*

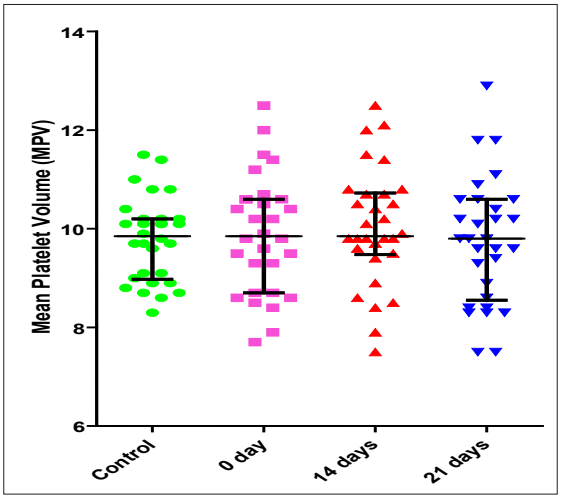

Fig21. *Median (IQR) of mean platelet volume (MPV) in control and during COVID-19 Virus Infection among COVID-19 Patients*

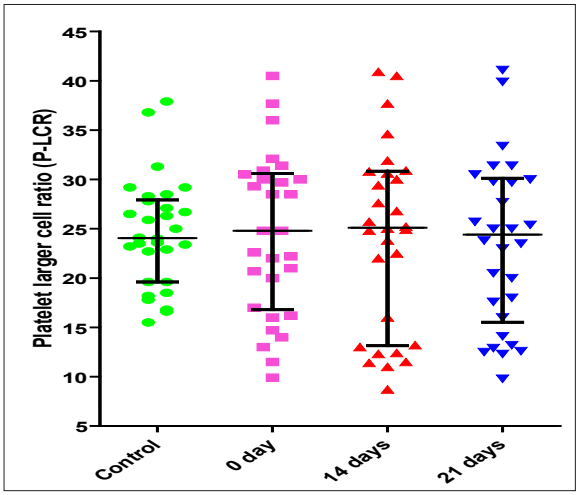

Fig22. *Median (IQR) of platelet large cell ratio (P-LCR) in control and during COVID-19 Virus Infection among COVID-19 Patients*

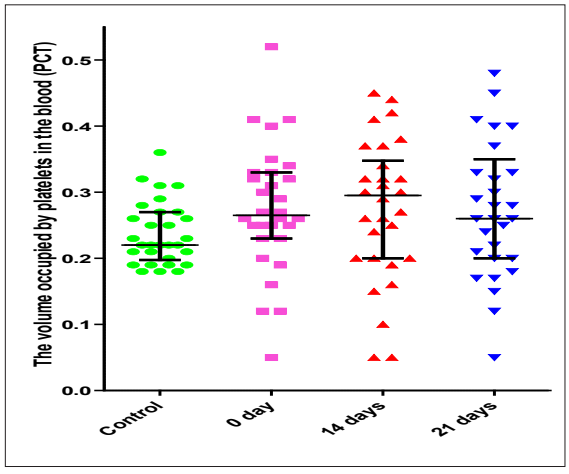

Fig23. *Median (IQR) of the volume occupied by platelets in the blood (PCT) in control and during COVID-19 Virus Infection among COVID-19 Patients*

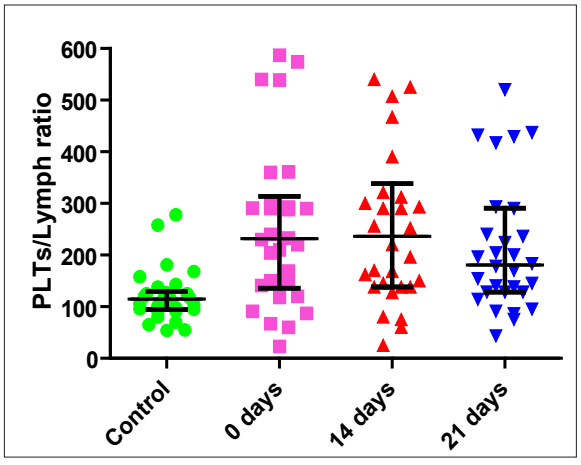

Fig24. *Median (IQR) of platelets/lymphocytes ratio (PLTs/Lymph ratio) in control and during COVID-19 Virus Infection among COVID-19 Patients*

The percentages of corona virus infected patients with thrombocytopenia (<150 x 10^3/µL) was 13.3%, 16.7%, and 10% at 0 day, 14 days, and 21 days of hospital admission, respectively (Table. 6& Figure. 25).

Table6. *Frequency and percentage of coronavirus infected patients with <150 x 103/µL& ≥150 x 103/µL Platelets count at different periods of infection.*

Parameter	Groups	0 day Frequency (%)	14 days Frequency (%)	21 days Frequency (%)
Platelets count (x 10^3/µL)	<150 x 10^3/µL	4 (13.3)	5 (16.7)	3 (10)
	≥150 x 10^3/µL	26 (86.7)	25 (83.3)	27(90)

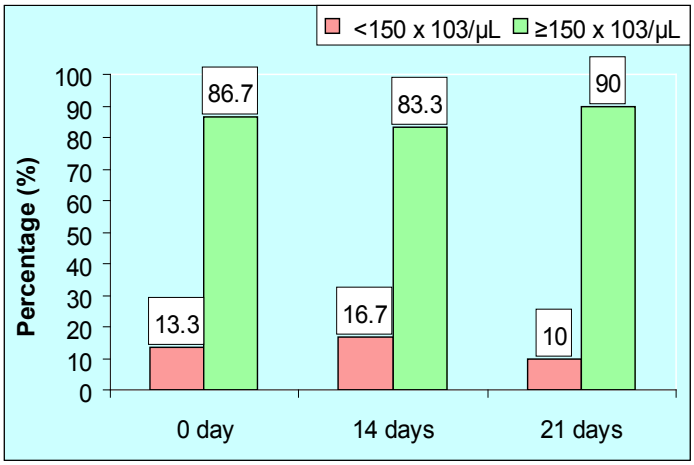

Fig25. *Percentage of coronavirus infected patients with <150 x 103/µL& ≥150 x 103/µL Platelets count at different periods of infection.*

Correlation Between Age & Haematological Parameters in Covid-19 Patients

The data in (Table .7) show the correlation between age & haematological parameters in coronavirus infected patients. This correlation appeared as a significant positive correlation between age of patients and WBCs count (P=0.000), RDW-SD (P=0.000), RDW-CV (P=0.000), Hemoglobin (P=0.002), Hematocrit (P=0.001), MCV (P=0.036), PDW (P=0.037), and P-LCR (P=0.038), and a significant negative correlation between age and MXD% (P=0.003), and a none significant correlation between age and the other hematological parameters.

Table7. *Correlation between age & haematological parameters*

Parameters	Spearman r	P value (two-tailed)	P value summary
WBCs	0.455	0.000	***
Lymphocytes %	0.054	0.702	ns
Neutrophils %	-0.025	0.860	ns
MXD%	-0.397	0.003	**
RBCs	0.245	0.071	ns
Hemoglobin	0.404	0.002	**
Hematocrit	0.430	0.001	**
MCV	0.284	0.036	*
MCH	-0.038	0.785	ns
MCHC	-0.197	0.150	ns
RDW-SD	0.553	0.000	***
RDW-CV	0.490	0.000	***

Platelets	-0.104	0.449	ns
PDW	0.292	0.037	*
MPV	0.207	0.144	ns
P-LCR	0.292	0.038	*
PCT	0.041	0.759	ns

ns: none significant correlation, (*) significant correlation at (P<0.05), (**) significant correlation at (P<0.01), (***) significant correlation at (P<0.001).

Correlation Between Wbcs, Lymphocytes %, Neutrophils, and Mxd% & Different Haematological Parameters in Covid-19 Patients

The data in (Table .8) show the correlation between WBCs count, Lymphocytes %, Neutrophils %, and MXD% & different haematological parameters in COVID-19 Patients. This correlation appeared as a significant positive correlation between WBCs count and Neutrophils % (P=0.044), RBCs count (P=0.003), hemoglobin concentration (P=0.000), Hematocrit (P=0.000), RDW-SD (P=0.005), RDW-CV (P=0.043), PDW (P=0.021), and P-LCR (P=0.043), and a significant negative correlation between WBCs count and MXD% (P=0.000), Platelets count (P=0.018), and PCT (P=0.032) and a none significant correlation with the other hematological parameters.

This correlation appeared as a significant positive correlation between lymphocytes % and MXD% (P=0.000), and a significant negative correlation with Neutrophils % (P=0.000), and a none significant correlation with the other hematological parameters.

Table. 8 show a positive correlation between Neutrophils % and WBCs count (P=0.044), a significant negative correlation with Lymphocytes % (P=0.000) and MXD% (P=0.000), and a none significant correlation with the other hematological parameters. Also, data in the same table show a positive correlation between MXD% and Lymphocytes % (P=0.000), a significant negative correlation with WBCs count (P=0.000), Neutrophils % (P=0.000), RBCs count (P=0.007), Hemoglobin concentration (P=0.001), Hematocrit value (P=0.000), RDW-SD (P=0.025), RDW-CV (P=0.037), and PDW (P=0.012), and a none significant correlation with the other hematological parameters.

Table8. *Correlation between WBCs, Lymphocytes %, Neutrophils, and MXD%& different haematological parameters in COVID-19 Patients*

Parameters	WBCs			Lymphocytes %			Neutrophils %			MXD%		
	Spearman r	P value (two-tailed)	P value summary	Spearman r	P value (two-tailed)	P value summary	Spearman r	P value (two-tailed)	P value summary	Spearman r	P value (two-tailed)	P value summary
WBCs count	-	-	-	-0.287	0.066	ns	0.308	0.044	*	-0.640	0.000	***
Lymphocytes %	-0.287	0.066	ns	-	-	-	-0.954	0.000	***	0.522	0.000	***
Neutrophils	0.308	0.044	*	-0.954	0.000	***	-	-	-	-0.666	0.000	***
MXD%	-0.640	0.000	***	0.522	0.000	***	-0.666	0.000	***	-	-	-
RBCs count	0.432	0.003	**	-0.088	0.436	ns	0.140	0.212	ns	-0.297	0.007	**
Hemoglobin	0.689	0.000	***	-0.106	0.349	ns	0.141	0.209	ns	-0.370	0.001	**
Hematocrit	0.609	0.000	***	-0.134	0.238	ns	0.171	0.126	ns	-0.388	0.000	***
MCV	0.038	0.802	ns	0.076	0.504	ns	-0.058	0.608	ns	-0.074	0.509	ns
MCH	-0.066	0.665	ns	0.218	0.052	ns	-0.219	0.050	ns	0.115	0.305	ns
MCHC	-0.061	0.692	ns	0.127	0.261	ns	-0.141	0.210	ns	0.083	0.459	ns
RDW-SD	0.417	0.005	**	-0.179	0.116	ns	0.192	0.089	ns	-0.253	0.025	*
RDW-CV	0.311	0.043	*	-0.190	0.095	ns	0.203	0.073	ns	-0.235	0.037	*
Platelets count	-0.350	0.018	*	0.092	0.419	ns	-0.123	0.274	ns	0.215	0.054	ns

PDW	**0.351**	**0.021**	*	**-0.091**	**0.435**	**ns**	**0.142**	**0.219**	**ns**	**-0.284**	**0.012**	*
MPV	**0.300**	**0.051**	**ns**	**-0.015**	**0.895**	**ns**	**0.040**	**0.727**	**ns**	**-0.224**	**0.051**	**ns**
P-LCR	**0.310**	**0.043**	*	**0.027**	**0.815**	**ns**	**-0.004**	**0.975**	**ns**	**-0.182**	**0.113**	**ns**
PCT	**-0.317**	**0.032**	*	**0.110**	**0.349**	**ns**	**-0.131**	**0.264**	**ns**	**0.143**	**0.220**	**ns**

ns: none significant correlation, (*) significant correlation at (P<0.05), (**) significant correlation at (P<0.01), (***) significant correlation at (P<0.001).

Discussion

The guidelines of the National Health Commission of China for COVID-19 5th Edition [22, 23] and the WHO interim guidance [22, 24] currently recommended two laboratory parameters- normal/decreased numbers of leucocytes or decreased number of lymphocytes as one of the criteria for the diagnosis of COVID-19 infection. Yousif et al., [3] reported that the mean of three hematological markers significantly increased with a mild sign (P =0.005, 0.002&0.005) for hemoglobin, WBC & platelets respectively. Moreover, by using the Kaplan-Mier test the mortality rate of COVID-19 patients increased with low levels of three hematological marker concentration during a maximum of 4weeks of follow up periods post-diagnosis. The three hematological markers show a good test to predict patients with severe cases. From these findings, authors concluded that high expression of platelets, hemoglobin, and WBCs correlates with the surviving rate and may be used as the prognostic marker. Lymphopenia in covid-19, seems to be the most relevant peripheral hematopoietic alteration, its use being suggested as a severity biomarker of the infection. In this context, studies related to the evaluation of biomarkers of hematological parameters that can be used as screening for exam diagnosis, as well as monitoring the evolution of severe cases, when necessary [21, 25]. Lymphopenia is a common feature in the patients with COVID-19 and might be a critical factor associated with disease severity and mortality [26]. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio may also have prognostic value in determining severe cases [8].

The current study showed that corona virus infection caused a significant decrease in hemoglobin concentration, MCH, MCHC, lymphocytes %, and mixed %, and a significant increase in RDW-SD, RDW-CV, leukocytes count, and neutrophils %, ratio at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals. Also, the present study showed that the percentages of corona virus infected patients with leukopenia was 3.3% at 0 day and 14 days of hospital admission, anemia was 26.7%, 16.7%, and 33.3%, leukocytosis was 60%, 56.7, and 50%, lymphocytopenia was 63.3%, 56.7%, and 43.3% and neutrophilia was 76.7%, 76.7%, and 60% at 0 day, 14 days, and 21 days of hospital admission, respectively. Simillar results were recorded in some of the previous studies. Leucocytosis, especially neutrophilia, is a SARS-CoV2 infection-induced alteration detectable at the CBC of COVID-19 patients [27-33]. In the Chinese population, Duarte et al., [21], and Fan et al., [34] studies have reported the presence of leucopenia on hospital admission, basically at the expense of moderate to severe lymphopenia and mild thrombocytopenia, as well as a decrease in hemoglobin, absolute monocyte count and even tend to develop neutrophilia during hospitalization, with a peak in this period of ICU stay. Analysis of the baseline CBC parameters of the study population showed that 4 cases (12.9%) showed neutrophilia, 3(9.6%) cases showed lymphopenia, and 5 cases (16.1%) showed monocytosis. However, the baseline total leucocyte count was not increased [22]. In contrast to the other studies conducted in China, whereby 63% of cases showed lymphopenia and 42% cases outside the Chinese population [28, 30]. Fan et al., [34] reported that on admission of the COVID-19 patients to the national centre for infectious diseases (NCID), leukopenia (WBC ≤4 x 109/L) was observed in 19 patients (29.2%) with only one patient presenting with severe leukopenia (WBC < 2 x 109 /L). Lymphopenia featured in 24 patients (36.9%) with 19 having moderate lymphopenia (Absolute Lymphocyte Count (ALC) 0.5 – 1 x 109/L) and 5 with severe lymphopenia (ALC <0.5 x 109/L). 28% of all patients presented with lymphopenia (ALC<1 x 109/L). Lymphopenia featured prominently in COVID-19 ICU group with a median nadir ALC of 0.4 x 109/L compared to 1.2 x 109/L in the non-ICU group. Monitoring of such hematologic parameters may help to identify patients who may need ICU care. An ALC approaching severe lymphopenia of <0.6 x 109/L may possibly be considered as one of the indicators for early admission for supportive care in the ICU. Notably, ICU patients tend to develop neutrophilia during the hospitalization with a median peak Absolute Neutrophil Count (ANC) of 11.6 x 109/L, compared to

3.5 x 109/L in the non- ICU group (p value < 0.001). Most patients had normal platelet counts with 13 patients (20.0%) having mild thrombocytopenia (platelet count 100 – 150 x 109/L). The median nadir platelet count remained in the normal range (above 150 x 109/L) for both groups and was not a discriminating test on admission or during the hospitalization. Tiwari et al., [22] reported that the majority of the COVID-19 patients admitted to Super Speciality Pediatric Hospital & Post Graduate Teaching Institute NOIDA, from March to April, are younger and have mild clinical presentation with female predominance. Pediatric cases have mild symptomology. Baseline CBC findings of all the cases show mild neutrophilia, mild lymphopenia, eosinopenia, mild monocytosis, and a normal to mild thrombocytopenia. An increase in CBC parameters, neutrophil-lymphocyte ratio (NLR), was noted in follow up cases. Anemia was not noted in baseline CBC and in follow up group. A onetime platelet lymphocyte ratio (PLR) is not indicative of disease progression. A significant statistical trend of increase in CBC parameters, NLR, was noted in follow up cases with persistent symptoms; however, a larger follow-up cohort is needed to arrive at a statistical significance. The CBC parameters in a COVID case show neutrophilia, leucocytosis, lymphopenia, and thrombocytopenia [35]. Huang et al., [36] and Yang et al., [37] mentioned in their articles whereby 85% of the critically ill patients of their study group with COVID-19 showed lymphopenia. The presence of lymphopenia as a signature of severe COVID-19 was confirmed by Bai et al., [38] who reported that ICU patients suffering this infection had a median lymphocyte count of 800 cells/mm with -non-survivors exhibiting persistent lymphopenia. Also, Lippi and Plebani, [30] carried out a systematic literature review and highlighted that the most important hematological parameter abnormalities observed in COVID-19 patients, which may predict the progression toward severe or critical forms of COVID-19, include leukocytosis, neutrophilia, and lymphopenia. Each of these prognostic parameters retains a specific clinical and biological significance, which, altogether, can contribute to reflect the evolution toward more unfavorable clinical pictures. In Chinese study, Xu et al., [39] reported that eosinopenia is a significant prognosticating factor, and a potentially more reliable laboratory predictor of SARS-CoV-2 infection than recommended leukocyte counts and lymphopenia.

Researchers speculated multiple reasons for a decrease in lymphocyte numbers that may have occurred due to direct infection, inflammation, or inhibition by metabolic disorders. They state that these associations can be crucial in prioritizing patients with severe disease so that treatment therapies can be initiated at the earliest [3, 4, 18, 40-43]. A substantial decrease in the total number of lymphocytes could be used as an index in the diagnosis of 2019-nCoV infection, indicating a consumption of immune cells and an impairment to cellular immune function (44, 45). Non-survivors developed more severe lymphopenia over time [45, 46]. Several factors may contribute to COVID-19 associated lymphopenia. It has been shown that lymphocytes express the ACE2 receptor on their surface [8, 39]; thus SARS-CoV-2 may directly infect those cells and ultimately lead to their lysis. Furthermore, the cytokine storm is characterized by markedly increased levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein [8, 47], MCP-1, MIP1-a) and tumor necrosis factor (TNF)-alpha, which may promote lymphocyte apoptosis [8, 47-49]. The virus might directly destroy lymphatic organs. Pro-inflammatory cytokines, such as IL-6 and TNF-alpha, could induce lymphocyte deficiency [33, 49]. Substantial cytokine activation may be also associated with atrophy of lymphoid organs, including the spleen, and further impairs lymphocyte turnover [8, 50]. Coexisting lactic acid acidosis, which may be more prominent among cancer patients who are at increased risk for complications from COVID-19 [8, 51], may also inhibit lymphocyte proliferation [8, 52]. A study conducted by Qin et al. [28] showed that primary dysregulation of the immune response, especially T lymphocytes, might be highly involved in the pathological process of COVID-19. Most of the severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. The number of T cells significantly decreased, and more hampered in severe cases [38].

The neutrophil-lymphocyte ratio (NLR) is an inflammatory biomarker that can be used as an indicator of systemic inflammation; the NLR is defined by the absolute number of neutrophils divided by the absolute number of lymphocytes. It is a simple measure that does not add costs to complete blood count laboratory examinations, which are performed

routinely in hospitals. The NLR has been tested as a guide for the prognosis of various diseases, such as cancer, community pneumonia and sepsis (53-56). NLR, and platelet-to-lymphocyte ratio (PLR) have been investigated as independent predictors for prognosis of systematic inflammatory diseases [57-59]. Also, some authors proposed neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for severe disease [32, 33, 42, 60].

The current study showed that corona virus infection caused a significant increase in neutrophils/ lymphocytes ratio, and Platelets/Lymphocytes ratio at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals. Similar result was recorded by Ciaccio and Agnello, [33] who reported that the NLR were elevated in COVID-19 patients, that resulting from the increased neutrophil count and decreased lymphocyte count, and significantly associated with an increased risk of all-cause death during hospitalization of COVID-19 patients. NLR was more useful to predict severity as well as IL-6 to predict prognosis of COVID-19. PLR and LMR were initially found to be higher in SARS-CoV-2 virus-infected group than in influenza A [61]. The PLR of patients means the degree of cytokine storm, which might provide a new indicator in the monitoring in patients with COVID-19 [62].

COVID-19 infected patients, whether hospitalized or ambulatory, are at high risk for venous thromboembolism, and an early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin is highly recommended [8].

The current study showed that a none significant changes in median platelets count in patients infected with corona virus compared with the controls. The results also showed that a corona virus infection induced a thrombocytopenia with 13.3%, 16.7%, and 10% at 0 day, 14 days, and 21 days of hospital admission in COVID-19 patients, respectively. These results run parallel to this carried out by Chen et al., [63] who reported that a 38-year-old man developed cough and dyspnea, followed by fever and muscle aches. On the 13th, he attended the outpatient department of the Union Hospital, Wuhan. A chest CT scan showed multiple densities of ground glass, a blood test showed a normal platelet count (196 × 10^9 cells per L), and the COVID-19 nucleic acid test was positive. On day 20, all other laboratory tests were within the normal reference range. Differential diagnosis included acute complications COVID-19 infection and immune thrombocytopenia after infection. Thrombocytopenia has been shown to occur in patients with COVID-19, usually reported on admission to hospital, although thrombocytopenia later occurred in the course of the disease. The efficacy of immunoregulatory therapy, varying B. bone marrow aspiration suggest immune thrombocytopenia in this patient, and normal prothrombin time and partial activated thromboplastin time suggest that other coagulation abnormalities were not the cause of the severe thrombocytopenia.

Conclusion

It can be concluded that coronavirus infection caused a significant decrease in hemoglobin, MCH, MCHC, lymphocytes %, mixed %, and a significant increase in RDW-SD, RDW-CV, leukocyte count, neutrophils %, and neutrophils/lymphocytes ratio in patient compared to the controls. There were a significant correlation between age, WBCs count, lymphocytes %, neutrophils %, MXD% and some haematological parameters. The effects of coronavirus infection on hematological alterations are still poorly understood so, further haematological studies are needed to confirm this results. These haematological changes may help the clinicians to better understand the COVID-19 and provide more clinical treatment options.

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