

Role of RBC Indices as Prognostic Markers in COVID-19 Patients

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Abstract

Background: SARS-CoV-2 triggers severe immune responses causing organ damage. It was detected in December 2019 and emerged as a global respiratory threat. Complete blood count (CBC) is crucial for assessing health, including RBC count, MCV, MCHC, MCH, and RDW.

Objectives: The study aimed to analyze RBC-related parameters and their response to COVID-19 infection.

Patients and methods: A case-control study including 200 with moderate COVID-19 cases and 100 controls who were healthy individuals of the same sex and age group. Blood samples were collected for various tests, including CBC, ferritin, CRP, LDH, PT, and D-Dimer. RT-PCR was used for SARS-CoV-2 detection from nasopharyngeal swabs.

Results: In contrast to the control group, COVID-19 patients had significantly lower RBCs ($P=0.002$), hemoglobin ($P=0.001$), hematocrit value ($P=0.005$), MCHC ($P=0.005$), lymphocyte percentage ($P=0.005$), and lymphocyte count ($P=0.001$). However, they had significantly higher RDW, Neutrophil percentage, D-dimer, CRP, ferritin, and LDH than the control group. Patients showed marginally significant positive correlations between MCH and D-Dimer ($P=0.011$), RDW and LDH ($P=0.007$), and marginally significant negative correlations between RBCs and LDH ($P=0.011$).

Conclusion: Patients with COVID-19 showed higher levels of RDW, CRP, ferritin, and LDH, but lower levels of RBC count, hemoglobin, hematocrit, MCHC, and lymphocyte count, indicating that these markers offer valuable insights into the prognosis of COVID-19 patients. There were positive correlations between MCH and D-Dimer and between RDW and LDH. While there were negative correlations between Hb, RBCs, and LDH.

Keywords: RBC Indices; Inflammatory markers; COVID-19.

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Introduction

The severe acute respiratory syndrome-associated Coronavirus 2 (SARSCoV-2) infection triggers an exaggerated immune response, resulting in extensive damage to various organs and the potential for severe respiratory syndrome and fatal outcomes (Huang et al., 2020).

In December 2019, the Chinese Center for Disease Control and Prevention initially detected this novel coronavirus in throat swab samples from patients experiencing unexplained pneumonia symptoms characterized by dry cough, dyspnea, and fever. SARS-CoV-2, categorized as a single-strand RNA virus within the Coronaviridae family, emerged as the primary causative agent of global respiratory symptoms following the Wuhan outbreak in January 2020 (Wu et al., 2020).

For decades, the complete blood count (CBC) has played a pivotal role in assessing individuals' overall health status. Within the CBC, specific blood indices hold significance: the total red blood cell (RBC) count, crucial for understanding bone marrow's production capacity; mean corpuscular volume (MCV), reflecting cell size; mean corpuscular hemoglobin (MCH); and cell distribution width (RDW), indicating variations in RBC size (Zhang et al., 2020). RDW, an easily accessible laboratory parameter available through modern hematology analyzers, serves as a measure of anisocytosis, a condition characterized by substantial heterogeneity in circulating erythrocyte volumes (Lippi et al., 2016).

In critically ill patients with sepsis, baseline RDW emerges as a significant and independent predictor of mortality (Zhang et al., 2020). Additionally, an association between elevated RDW and reduced ventilator-free days in intensive care unit

patients was established (Otero et al., 2018).

The study aims to evaluate RBC-related parameters and their response to COVID-19 infection.

Patients and Methods

In the Clinical Pathology Department of Qena University Hospital, this case-control study was conducted during the year 2022, spanning from January to December. The study enrolled adult patients who sought medical attention at the emergency department during this period involving 200 adults with moderate severity COVID-19, presented with fever, cough, lethargy, upper respiratory symptoms, and/ or headache, loss of taste or smell and lower respiratory symptoms (WHO, 2021).

Inclusion criteria: adults older than 18 years old of both sexes who presented to the emergency department and were diagnosed with COVID-19 through polymerase chain reaction (PCR) testing.

Exclusion criteria: patients with negative COVID-19 PCR results, a history of hemolytic anemia, a history of previous chronic hematologic disease, and children.

The study aimed to evaluate changes in red blood cells (RBC) and RBC-related indices in response to moderate COVID-19 infection.

Ethical approval was obtained from the local institutional Ethical Research committee (Approval Code: SVU-MED-CCPO31-1-21-11-272) and informed written consent was obtained from all patients.

Laboratory investigations

- **Blood sampling:** 6 ml of venous blood was collected and divided into 3 tubes.
- 2 milliliters of blood were placed in an EDTA vial for a complete blood count (CBC) using Cell Dyn Ruby (Abbott Diagnostics, Santa Clara, California, USA). These were the reference values:

Red Blood Cell Count (men: $4.0- 5.9 \times 10^6/\mu\text{L}$; women: $3.8- 5.2 \times 10^6/\mu\text{L}$), Hemoglobin (men: 13.2-16.6 g/dl; women, 11.6-15 g/dl), Hematocrit (men: 38.3-48.6%; women: 35.5-44.9%), Mean corpuscular volume (MCV: 76-100 fl/cell), Mean corpuscular hemoglobin (MCH) (27-34 pg/cell), Mean corpuscular hemoglobin concentration (MCHC) (32-35 g/dl), white blood cell (WBCs) count with a reference value of ($3.5-10 \times 10^3/\text{mm}$), platelet (PLT) count ($150-400 \times 10^3/\text{mm}$).

- 2 milliliters of blood were placed in a sodium citrate tube and coagulation was assessed within two hours using a coagulation analyzer (Sysmex (CS-1600) Dade Behring, Kobe-Japan). Plasma samples were obtained by centrifugation at 2000 g for 10 minutes to evaluate prothrombin time (PT) by coagulation assay (normal value: 10-13.6 sec) and D-Dimer by particle-enhanced immunoturbidimetric assay (normal value ≤ 500 ng/ml).
 - To obtain serum samples, 2 ml blood was placed in a plain tube and allowed to clot at 37°C. The tube was then centrifuged at 3000 g for 10 minutes at room temperature. Serum was used to assess ferritin level utilizing Automated Enzyme Immunoassay System (AIA-360) Tosoh (Tokyo-Japan) with reference value of 15-150 ng/ml, C-reactive protein (CRP) level was measured by latex-enhanced immunoturbidimetric assay with reference value of < 6 mg/L), and lactate dehydrogenase (LDH) levels were measured utilizing Beckman Coulter AU 480-CA-USA system. There reference value for LDH was 225-450 U/L
- b) Nasopharyngeal swabs were collected by inserting a sterile swab into the nostril of the patient over the surface of the posterior nasopharynx and then rotated 3-4 times against the nasopharyngeal

surface. Then withdraw the swab from the nasal cavity. Qualitative detection of nucleic acid from SARS-CoV-2, the virus responsible for COVID-19, was achieved through reverse-transcriptase real-time polymerase chain reaction (RT-PCR). This was performed on samples collected from patients' nasopharyngeal swabs (NPS) using the fully automated, spin-column-based nucleic acid extraction technique, QIA cube Connect (QIAGEN in Hilden, Germany). Reaction amplification conditions and result interpretation adhered to manufacturer instructions, employing the Roto-gene Q system.

Statistical analysis

The data was analyzed utilizing the Statistical Package for Social Sciences (SPSS) tool, specifically version 24, which is software developed by IBM Corporation, located in Armonk, NY, USA. Levin test was used for data normality testing. Based on the obtained data, the qualitative variables were documented in terms of frequencies and percentages, and their comparison will be conducted using the chi-square test. The quantitative measures were reported as means \pm standard deviation (SD) and were subjected to comparison using the student t-test. Pearson correlations were used to study the correlation between different parametric variables. For all tests, a (two-tailed) p-value less than 0.05 were deemed to be statistically significant.

Results

Our study included 200 adults having COVID-19 positive PCR and 100 healthy controls. The mean age of patients was 53 ± 17.8 years 152 females (76%) and 48 males (24%), from which there were 67 patients (33.5%) under the age of 40 years and 133 patients (66.5%) over the age of 40 years. The mean age of the control group was 33.6 ± 11.6 years, 62 females (62%) and

38 males (38%) from which there were 78 (78%) under the age of 40 years and 22 (22%) over the age of 40yr, (Table.1).

Table 1. Age and Sex of the studied groups

Variables	Patients (200)	Controls (100)	P. Value
Male N (%)	48 (24%)	38 (38%)	0.011^{*x}
Female N (%)	152 (76%)	62 (62%)	0.011^{*x}
Under the Age of 40 years	67 (33.5%)	78 (78%)	< 0.001^{*x}
Over the Age of 40 years	133 (66.5%)	22 (22%)	< 0.001^{*x}
Mean age (years)	50 ± 16.74	33.68 ± 11.52	< 0.001^{*t}

*: significant If P< 0.05, x: Chi square test, t: t-test

All COVID-19 patients, 100%, exhibited fever and cough as primary symptoms. Other symptoms were sore throat (91%), nasal congestion (89.5%), fatigue

(87.5%), chest pain (75.5%), headaches (74%), loss of smell (72%), shortness of breath (69%), Loss of taste (66.5%), and runny nose (63.5%), (Fig.1).

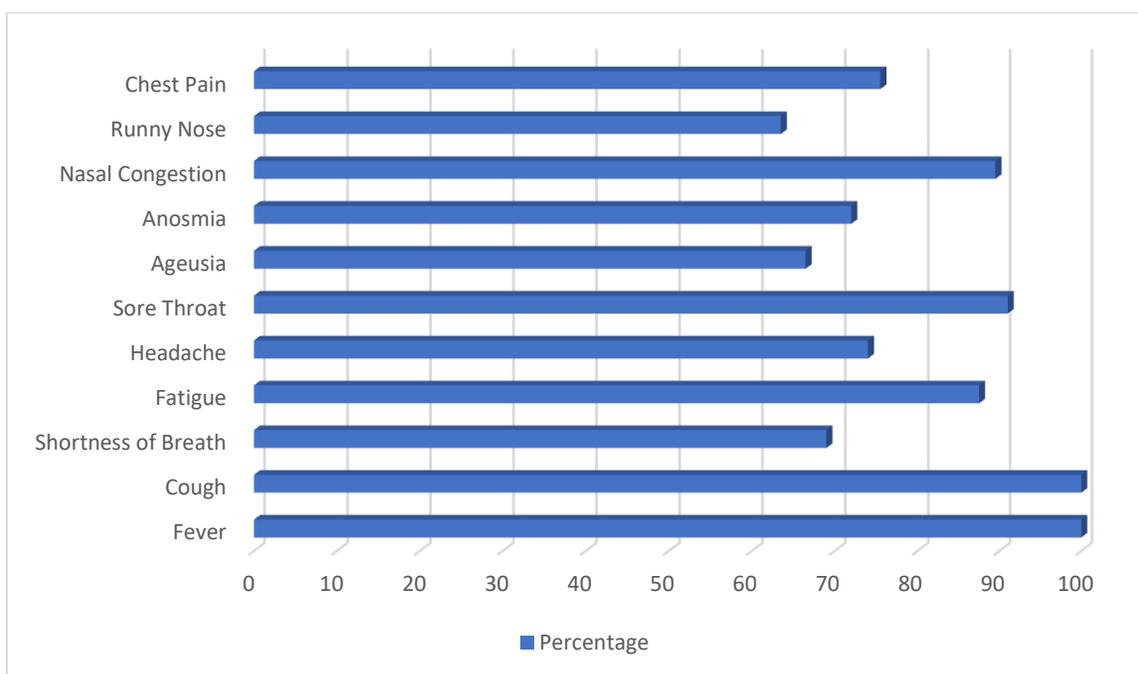


Fig.1. Symptoms reported among all COVID-19 patients.

Laboratory Data

Compared to the healthy controls, patients had significantly lower levels of RBC count (P = 0.002), Hb (P = 0.001), Hct (P = 0.005), MCHC (P = 0.005), lymph percentage (P = 0.001), and absolute lymph (P = 0.001), and PC (P = 0.001). While the patients had significantly higher values of

RDW, neutrophil percentage, PT, INR, D-dimer, CRP, Ferritin and LDH all have (P < 0.001). Compared to the healthy controls, patients had insignificantly lower MCH (P = 0.188), and PLT (P = 0.536) while had non-significantly higher MCV (P = 0.649), WBCs (P = 0.709), and absolute neutrophil (P = 0.616), (Table. 2).

Table 2. Laboratory Values of Patients and Controls

Variables	Patients (200)	Controls (100)	P. Value
	Mean ± SD	Mean ± SD	
RBCs (10 ⁶ /μL)	4.6±0.7	4.9±0.6	0.002*
Hb (g/dl)	12±1.8	13.4±1.6	0.001*
Hct (%)	38.4±5.6	40.6±5.1	0.005*
MCV (fl/cell)	84±5.5	83.7±5.3	0.649
MCH (pg/cell)	27±2	27.7±2.3	0.188
MCHC (g/dl)	32±1.3	33±1.7	0.005*
RDW (%)	14.5±1.3	13±1.2	0.001*
WBCs (*10 ³ /mm)	7.5±3.5	7.3±2.2	0.709
%Neutrophil	73±13	54±10	0.001*
# Neutrophil (*10 ³ /μL)	5.7±3.3	4.2±1.8	0.616
% Lymph	20.4±12	34±9.6	0.001*
# Lymph (*10 ³ /μL)	1.3±0.7	2.4±0.7	0.001*
PLT (*10 ³ /mm)	262±98	270±78.1	0.536
MPV (fL)	9±1.2	9±1.6	0.955
PT (sec)	19.5±2.2	13.3±0.9	0.001*
PC (%)	44±7.2	89±9.4	0.001*
INR	1.8±0.2	1.1±0.1	0.001*
D-dimer (ng/ml)	994±178	82.3±68	0.001*
CRP (mg/l)	605±170	39±12	0.001*
Ferritin (ng/ml)	417±72	104±26	0.001*
LDH (U/L)	499±86.6	317±61	0.001*

*: significant; t: t-test

RBCs: Red Blood Cells, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Cell Distribution Width, WBCs: White Blood Cells, % Neutrophil - Neutrophil Percentage, # Neutrophil: Absolute Neutrophil Count, % Lymph: Lymphocytes Percentage, #Lymph: Absolute Lymphocyte Count, PLT: Platelets count, MPV: Mean Platelet Volume, PT: Prothrombin Time, PC: Prothrombin concertation, INR: International Normalized, CRP: C-Reactive Protein and LDH Lactate Dehydrogenase.

Correlation

In COVID-19 patients, there was a weak positive correlation between MCH and D-Dimer (r = 0.18, p = 0.011), and between RDW and LDH (r = 0.19, p = 0.007), as

well as negative correlation between Hb and LDH (r = -0.205, p = 0.004) and RBCs and LDH (r = -0.179, p = 0.011), (**Table. 3, Fig.2**).

Table 3. Pearson Correlation between different laboratory variables in COVID-19 patients

Variables		Hb	MCV (fl)	MCH (pg)	MCHC (g/dl)	RDW (%)	RBCs (10 ⁶ /μL)
PT (sec)	r	0.021	-0.21	-0.015	-0.002	0.074	-0.018
	p	0.771	0.768	0.83	0.981	0.299	0.799
D Dimer (ng/ml)	r	-0.073	0.129	0.18	0.135	0.01	-0.072
	p	0.303	0.07	0.011*	0.057	0.888	0.312
CRP (mg/l)	r	0.119	0.025	-0.013	-0.075	-0.094	0.163

	p	0.094	0.721	0.851	0.292	0.186	0.021
Ferritin (ng/ml)	r	-0.016	0.036	0.029	-0.008	-0.014	-0.02
	p	0.822	0.612	0.684	0.914	0.846	0.777
LDH (unit/L)	r	-.205	-0.076	-0.014	0.09	0.19	-0.179
	p	0.004*	0.284	0.842	0.205	0.007*	0.011*

RBCs: Red Blood Cells, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Cell Distribution Width, PT: Prothrombin Time, CRP: C- Reactive Protein and LDH Lactate Dehydrogenase.

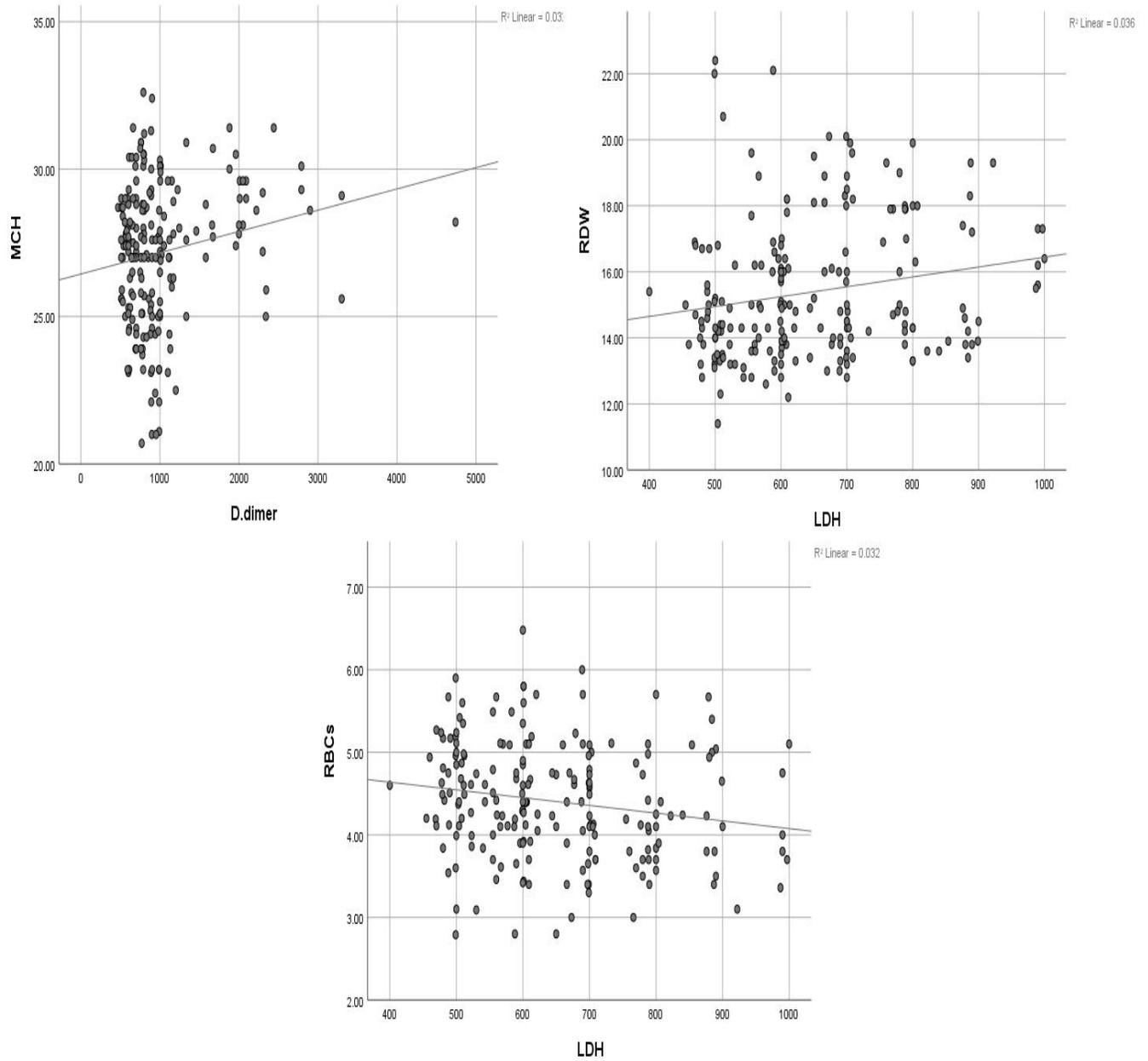


Fig.2. Pearson correlation between MCH and D-Dimer, RDW and LDH, RBCs and LDH in COVID-19 patients

Discussion

COVID-19 leads to a “cytokine storm” by the production of increased inflammatory cytokines such as IL-1B, IL-6, IL-12, IL-10, INF and MCP-1 which is manifested in the RBCs as increased oxidative stress which leads to accelerated RBC loss and is characterized by constitutional symptoms, systemic inflammation, and multi-organ dysfunction (Mullen et al., 2022). Lower values of RBC count are a sign of a worse prognosis in COVID-19, as well as a sign of increased comorbidities (Taneri et al., 2020).

In our study, COVID-19 patients vs. controls had significant lower RBC values ($p = 0.002$), lower hemoglobin ($P = 0.001$), this were in agreement with (Omrani-Nava et al., 2020; Yang et al., 2020; Aly et al., 2021; Jbireal et al., 2021), they also establish a correlation between COVID-19 severity and decreased hemoglobin levels. Kronstein-Wiedemann et al. (2022) reported that SARS-CoV-2 affects RBC progenitors. In contrast to our results, Fathalla et al., 2022 who reported insignificant negative correlation between Hb levels and severity of COVID-19, levels of CRP and LDH.

In our study, we found that MCH correlated positively with D-Dimer ($p = 0.011$). Mao et al. (2021) found lower MCH in severe COVID-19 cases, and Layla et al. (2021) linked lower MCV and MCH to poorer prognosis, in line with Anitha et al. (2021).

In our study, there was significantly lower MCHC in the patients group compared to the control group ($P=0.005$). This was in agreement with (Jbireal et al., 2021; Mao et al., 2021). However, Jeraiby et al. (2021) found insignificant changes, suggesting MCHC isn't a predictor in COVID-19.

In our study, patients had significantly higher RDW compared to the controls ($P=0.001$). This aligns with Ramachandran et al. (2021). An elevated RDW was associated with higher in-hospital mortality odds (Bellan et al., 2021) and increased mortality risk in COVID-19 patients (Weiss et al., 2019), indicating more severe illness and a proinflammatory state (Wang et al., 2021).

In our study, compared to controls, WBCs ($p = 0.709$) and neutrophil numbers ($p = 0.616$) showed insignificant differences, however, (Palladino, 2021) reported that higher counts indicate worse COVID-19 outcomes.

In the current study, Patients had higher neutrophil percentages compared to controls ($P < 0.001$), but significantly lower lymphocyte count and percentage ($p < 0.001$). These were in agreement with (Anurag et al., 2020; Aly et al., 2021). Lymphopenia is a common finding in COVID-19 critically ill patients, resulting from the direct destruction of lymphocytes, especially CD4+ T and CD8+ T cells (Chen et al., 2019), or cytokine-mediated lymphocyte destruction (Zheng et al., 2020).

We found significantly higher ferritin levels in patients compared to controls ($P = 0.001$). This was in line with, (Gandini et al., 2020; Huang et al., 2020; Kaushal et al., 2022). Moreover, Aly et al. (2021) reported higher ferritin levels in patients with positive correlation to COVID-19 severity and mortality rate. Elevated ferritin levels in COVID-19 cases indicate acute-phase response and inflammation, contributing to cytokine storms (Kernan and Carcillo, 2017) and macrophage activating syndrome (Shoenfeld et al., 2020).

We found that CRP levels are significantly higher ($P < 0.001$) in patients. It was reported that CRP is correlated with higher mortality risk, disease worsening, reliable treatment monitoring (Zhang et al., 2020), and worse COVID-19 prognosis (Ali, 2020; Aly et al., 2021).

In our study, patients had significantly higher LDH levels compared to controls ($P = 0.001$). There was a negative correlation between RBCs and LDH ($r = -0.179$, $p = 0.011$), and a positive correlation between RDW and LDH ($r = 0.19$, $p = 0.007$). This was in agreement with (Doghish et al., 2021, Chen et al., 2020; Fialek et al., 2022). Moreover, Henry et al. (2020) found that an increase in LDH of >16-fold increased mortality odds, while Han et al. (2020) linked an early increase in LDH levels to severe lung injury in COVID-19, due to cytokine-mediated lung tissue damage and LDH enzyme release (Martinez-Outschoorn et al., 2011). We found that patients had significantly prolonged PT, decreased PC, and increase in the INR ($P < 0.001$). This was in line with (Bohra et al., 2021). We found that patients had significantly higher D-dimer (0.001) compared to the controls and that D-dimer positively correlated with MCH ($r = 0.18$, $P = 0.011$). These are in agreement with (Rostami and Mansouritorghabeh, 2020; Long et al., 2020) reported that a worse COVID-19 prognosis is linked to higher D-dimer levels.

Conclusion

Patients with COVID-19 showed higher levels of RDW, CRP, ferritin, and LDH, but lower levels of RBC count, hemoglobin, hematocrit, MCHC, and lymphocyte count, indicating that these markers offer valuable insights into the prognosis of COVID-19 patients. There were positive correlations between MCH and D-Dimer and between

RDW and LDH. While there were negative correlations between Hb, RBCs, and LDH.

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