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Influence of COVID-19 on lymphocyte and platelet parameters among patients admitted to intensive care unit and emergency

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Abstract. – OBJECTIVE: The aim of the study was to detect the effect of COVID-19 on lymphocyte and platelet parameters among Sudanese patients admitted to Intensive Care unit (ICU) and emergency (ER).

PATIENTS AND METHODS: This cross-sectional study was carried out on a total of 787 Sudanese individuals (487 confirmed COVID-19 cases and 300 apparently healthy individuals as controls, in duration between April 2020 to December 2020). Platelets (PLTs) and platelet indices, mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT) and platelet larger cell ratio (PLCR) were investigated as part of the complete blood count (CBC) for the case and control group. Also, the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were calculated, and the results were statistically analyzed by SPSS version 21.

RESULTS: The severity of the disease was also affected by the patient's age: 262 COVID-19 cases admitted to ICU were over 50 years old, compared to only four patients in the mild group. Regarding hematological parameters, the absolute lymphocyte count, PLTs, MPV, PDW, and P-LCR were significantly different between cases and control groups (*p*-values = 0.000, 0.002, 0.000, 0.000, and 0.000, respectively). PLR and NLR levels were found to be significantly higher as disease severity increased; *p*-values = 0.000 and 0.000, respectively. The study also demonstrated that lymphopenia was associated with severe COVID-19 infection (in 93% of ICU patients, 59.9% of ER, and 9% of the mild group), while thrombocytopenia was detected only among 30.8% of ICU patients.

CONCLUSIONS: Lymphopenia and thrombocytopenia are associated with severe COVID-19 infection. NLR and PLR were markedly increased with COVID-19.

Key Words:
COVID-19, Sudan, MPV, PDW, PLCR, PLR, NLR.

Introduction

The WHO has tentatively defined the coronavirus infectious disease 2019 (COVID-19) as a rapidly transmitted systemic disease that affects several body systems, primarily the hematopoietic system and hemostasis, as well as the respiratory, neurological, gastrointestinal, cardiovascular, and immune systems[1-3]. The causative agent of COVID-19 is an RNA virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[4]. Firstly, WHO denominated the pandemic as 2019-nCoV. It was renamed to (SARS-CoV-2) by the international committee on Taxonomy of Viruses[5]. COVID-19 has broad clinical features, like the unspecific symptoms: extreme high fever, dry cough, pharyngitis and diarrhea. Furthermore, it may be combined with

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mild to severe pneumonia, dyspnea, tachypnea, and troubled gas exchange that leads to severe lung dysfunction, ventilation required, shock, multi-organ failure, or even death[6]. WHO deems COVID-19 as a universal communal health emergency because it has speedily developed from an epidemic outbreak in Wuhan, China (December 2019) into a pandemic all around the world[7,8]. COVID-19 poses a serious challenge to healthcare systems worldwide due to its rapid spread, unspecific symptoms, unavoidable mode of transmission (person to person contact), a large number of asymptomatic carriers, and an increase in demand for intensive care for a previously unanticipated number of patients, while non-infected individuals are also affected by preventive actions (social distancing)[9]. Lymphocytes and platelet count are recommended as laboratory markers to predict the severity of COVID-19[10,11]. SARS-CoV-2 invades and destroys lymphocytes through the angiotensin converting enzyme 2 (ACE2) receptor on their membrane, leading to lymphopenia[12]. During the incubation period and early phase of COVID-19, the lymphocyte count is normal or slightly decreased; however, 7 to 14 days after the onset of the main symptoms, there is a generalized increase in inflammatory mediators (cytokine storm), resulting in marked lymphopenia and hyperactivation of platelets, which directly leads to thrombocytopenia[13]. In addition to that there is increasing in destruction of lymphocytes caused by massive cytokines storm such as interleukins and tumor necrosis factor-alpha[14-16].

Furthermore, there is atrophy in the lymphoid organs, thus leading to imbalanced lymphopoiesis[17]. Therefore, lymphocyte count and neutrophil lymphocyte ratio (NLR) follow-up are markers of inflammation[18]. Platelet lymphocyte ratio (PLR) is an independent prognostic marker for patients who have been hospitalized for an extended period of time [a higher cytokine storm activates more platelets, resulting in a higher (PLR)][19]. This study was conducted to demonstrate the association of lymphopenia, thrombocytopenia, platelet parameters, NLR, and PLR with the severity of COVID-19.

Patients and Methods

This was a cross-sectional hospital-based study. Patients' demographic data (such as age and gender) was taken from the hospital's records. A total of 787 individuals participated in this study, 487 confirmed patients with COVID-19 admitted to the COVID-19 quarantine hospitals in Khartoum state, while 300 healthy volunteers used as control.

The research was conducted in period of March 2020 to December 2020. Age of participants ranged between 29 to 89 years. The patient group is further divided into three subgroups according to the severity of COVID-19 infection and the scores of patients at admission time: 273 patients in ICU, while 137 patients were admitted to ER, and 77 patients as mild (asymptomatic) group. The ICU subgroup involved COVID-19 patients with very severe symptoms who needed mechanical ventilation and intubation. The ER subgroup contained patients with less severe symptoms. In contrast, the mild subgroup included patients with very mild symptoms to asymptomatic (most of them were the isolated center's medical staff with confirmed COVID-19 infection). The study was approved by the Alzaiem Alazhari University Ethical Committee, and written informed consent was taken from each participant.

All COVID-19 patients were diagnosed by taking nasal swabs and tested using the real-time polymerase chain reaction device (RT-PCR), AccuPower® COVID-19 RT-PCR kit reagent (Bioneer Corporation, Daejeon, South Korea) following the manufacture guidance.

Sample Collection and Statistics

A total of 2.5 mL of EDTA-anticoagulated blood samples were collected from the control and case groups. CBC was done using an automated hematology analyzer (Sysmex KX-21N, Bath, UK). The measured parameters are the absolute lymphocyte count, platelet count (PLTs) and platelet indices like mean platelet volume (MPV), platelet distribution width (PDW), platelet crit (PCT) and platelet large cell ratio (P-LCR). The neutrophil lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Platelet Lymphocyte Ratio (PLR) was calculated by dividing PLTs count by the Absolute lymphocytes count[20,21]. SPSS version 21 (SPSS Corp., Armonk, NY, USA) was used to analyze the collected data for Mann-Whitney and Kruskal-Wallis tests, as well as the Chi Square test, which was used to obtain the frequencies and test the significance of the association, with a significant level set at (0.05). The median, maximum,

Table I. Gender distribution among different severity patient subgroups.

Study groups		Gender		Total
		Male	Female	
Patients' subgroups	ICU	188 (68.9%)	85 (31.1%)	273
	ER	88 (64.2%)	49 (35.8%)	137
	Mild	28 (36.4%)	49 (63.6%)	77
Total		454 (57.7%)	333 (42.3%)	787

and minimal values were achieved. The results were presented in the form of tables and figures (bar charts).

Results

This study included a total of 787 Sudanese individuals (487 confirmed COVID-19 cases by RT-PCR who were admitted to the COVID-19 quarantine hospitals in Khartoum state, Sudan, and 300 healthy individuals as a control group).

The present study demonstrated that among 487 COVID-19 patients, the male (62.4%) was more affected than the female (37.6%) as shown in (Table I). Furthermore, the patient's age had an effect on the severity of COVID-19: A total of 262 COVID-19 cases admitted to the ICU were over 50 years old, compared to only four patients in the mild group (Table II).

This study also showed that significant increases in the median of NLR, PLR, and P-LCR were 8.0, 219, and 25.0 %, respectively, among the case groups (p = 0.000, 0.000, and 0.000, respectively). Furthermore, results showed a decrease in the median of absolute lymphocyte count, PLTs, MPV and PDW among cases [1.0 (10^3 cell/µl), 234 (10^3 cell/µl), 9.9 fl and 12.4 fl, respectively], which revealed a significant difference between case and control group (p = 0.000, 0.002, 0.000 and 0.000, respectively), except in PCT (p = 0.862), (Table II).

Table II. Distribution of age groups among various severity patient subgroups.

Patients' subgroups	Age groups		Total
	Up to 50 years old	Above 50 years old	
ICU	11	262	273
ER	85	52	137
Mild	73	477	
Total	169	318	487

The results in this study showed that the absolute lymphocyte count was significantly decreased with disease severity (p = 0.000), while the PLR and NLR were significantly increased with disease severity (p = 0.000 and 0.000, respectively for all) (Table III). Comparison of analyzed lymphocyte and platelet parameters between different severity patient subgroups and the control group showed a highly significant result (p = 0.000) as displayed in Table IV.

The prevalence of lymphopenia, lymphocytosis, and normal lymphocyte count among patients of varying severity levels subgroups have been illustrated in (Table V) and have displayed highly significant results since (p = 0.000). The frequency of thrombocytopenia, thrombocytosis, and normal PLT count among different severity patient subgroups has shown highly significant results since (p = 0.000) (Table VI).

Table III. Comparison of the analyzed parameters between the patients and the control group.

Analyzed parameters	Case Median (Min-Max)	Control Median (Min-Max)	*p*-value
Absolute lymphocyte count (×10³cell/µL)	1.0 (0.09-17.8)	2.4 (1.1-5.6)	0.000**
PLTs (×10³cell/µL)	234 (23-821)	252 (183-460)	0.002**
MPV (fL)	9.9 (4.8-87.0)	10.8 (9.1-15.0)	0.000**
PDW (fL)	12.4 (8.8-23.3)	13.2 (10.3-22.1)	0.000**
PCT (%)	0.30 (0.1- 0.9)	0.30 (0.20-0.60)	0.862
P-LCR (%)	25.0 (9.4-51.3)	22.0 (13.1-40.9)	0.000**
NLR	8.0 (0.20-163)	1.3 (0.30-4.1)	0.000**
PLR	219 (2.5-2125)	102 (20-280)	0.000**

**$p \leq 0.001$ is highly significant.

Table IV. Comparisons between different severity patient subgroups and the control group.

Variables	ICU Median (Min-Max)	ER Median (Min-Max)	Mild Median (Min-Max)	Control Median (Min-Max)	*p*-value
Absolute lymphocyte count (×10³cell/µL)	0.6 (0.09-17.8)	1.3 (0.4-11.6)	2.2 (0.8-10.7)	2.4 (1.1-5.6)	0.000**
PLTs (×10³cell/µL)	206 (46-712)	245 (23-821)	271 (43-584)	252 (183-460)	0.000**
MPV (fL)	10.2 (5.9-87.0)	9.7 (5.5-17.6)	9.5 (4.8-17.1)	10.8 (9.1-15.0)	0.000**
PDW (fL)	12.9 (8.8-23.3)	12.0 (8.8-22.6)	11.4 (9.5-15)	13.2 (10.3-22.1)	0.000**
PCT (%)	0.20 (0.1-0.6)	0.30 (0.1-0.9)	0.30 (0.2-0.6)	0.30 (0.20-0.60)	0.862**
PLCR (%)	26.9 (9.4-51.3)	24.2 (9.7-45.3)	22.2 (13.1-40.9)	22.0 (13.1-40.9)	0.000**
NLR	15.0 (0.2-163)	4.9 (0.40-25)	1.8 (0.2-22)	1.3 (0.30-4.1)	0.000**
PLR	334 (3-2125)	180 (14-797)	127 (2.5-362)	102 (20-280)	0.000**

**$p \leq 0.001$ is highly significant.

Figure 1 displays the distribution of lymphocyte count among case subgroups, while Figure 2 illustrates the distribution of PLT count among case subgroups.

Discussion

This study was conducted to demonstrate the association of lymphopenia, thrombocytopenia, NLR, and PLR with the severity of COVID-19 in order to improve the disease outcome. This study included 304 (62.4%) male and 183 (37.6%) female; male was more common in ICU; 188 (68.9%) males *vs.* 85 (31.1%) females and ER; 88 (64.2%) males *vs.* 49 (35.8%) females; females were more common within mild subgroup 49 (63.6%) females *vs.* 28 (36.4%) males. This was semi-compatible with an Indian study[22] that reported COVID-19 incidence in male was 76%, but in female=46%. The present study showed that 262 patients admitted into the ICU unit had an age above 50 years old, 52 patients aged more than 50 were admitted to the ER unit, but only four patients aged above 50 years old had mild symptoms of COVID-19. This result was agreed with another research in Italy[23], which demonstrated that older age groups are more likely to get COVID-19 with more complications.

In the current study the absolute lymphocyte count resulted in a significant decrease with (*p*-value = 0.000). Also, the *p*-value showed significant variation in absolute lymphocyte count between all case subgroups (ICU, ER, and mild group). These results were close to those of a study in COVID-19 patients in China, which revealed a significant decrease in absolute lymphocyte count[24]. The current study showed the lymphopenia was predominant among the ICU

Table V. Prevalence of lymphopenia, lymphocytosis, and normal lymphocyte count among different patient severity subgroups.

Absolute lymphocyte count	Case group	Case subgroups			*p*-value
		ICU	ER	Mild	
Lymphopenia	345 (70.8%)	254 (93%)	82 (59.9%)	9 (11.6%)	0.000**
Normal lymphocyte count (1.2- 3.8×10³cell/µL)[25]	124 (25.5%)	12 (4.4%)	50 (36.5%)	62 (80.6%)	
Lymphocytosis	18 (3.7%)	7 (2.6%)	5 (3.6%)	6 (7.8%)	
Total	487	273	137	77	

**$p \leq 0.001$ is highly significant.

Table VI. Frequency of thrombocytopenia, thrombocytosis, and normal PLTs in various severity patient subgroups.

Variables	Case group	ICU	ER	Mild	*p*-value
Thrombocytopenia	112 (23%)	84 (30.8%)	25 (18.2%)	3 (3.9%)	0.000**
Normal PLTs (150-450×103cell/µL)[25]	349 (71.7%)	181 (66.3%)	99 (72.3%)	69 (89.6%)	
Thrombocytosis	26 (5.3%)	8 (2.9%)	13 (9.5%)	5 (6.5%)	

**$p \leq 0.001$ is highly significant.

and ER subgroup, so lymphopenia could be used as a prognostic marker for COVID-19. Our study is consistent with previous study[25] in COVID-19 patients admitted to ICU in the USA showing that lymphopenia was common (75%) in patients in ICU units. As previously stated, the COVID-19 lymphocyte count decreases 7 to 14 days after the onset of the main symptoms due to a generalized increase in inflammatory mediators, resulting in marked lymphopenia and hyperactivation of platelets, which directly leads to thrombocytopenia[13].

This study generally explained that there was a significant decrease in the median of PLT count between the case groups and also there were also significant differences in PLT count between the ICU and the control group, this is consistent with another study[26] in which PLTs showed significant differences between the case subgroups (ICU and ER).

Our study revealed a significant thrombocytopenia among the case groups; this finding was comparable to an American study[27] done on ICU patients with COVID-19 who showed severe thromocytopenia. The current study's thrombocytopenia was in conflict with a recent study conducted in China, which demonstrated an insignificant low platelet count (*p*-value 0.45)[28]; these variations in different studies may be due to the varied degree of COVID-19 severity on admission and the length of hospitalization period before testing.

The current research revealed a significant variation in platelet indices: significant increases in *P*-LCR median and a significant decrease in MPV and PDW. The result of MPV in this present study among the ICU subgroup agreed with another study was performed in COVID-19 patients in Salt Lake City. This study illustrat-

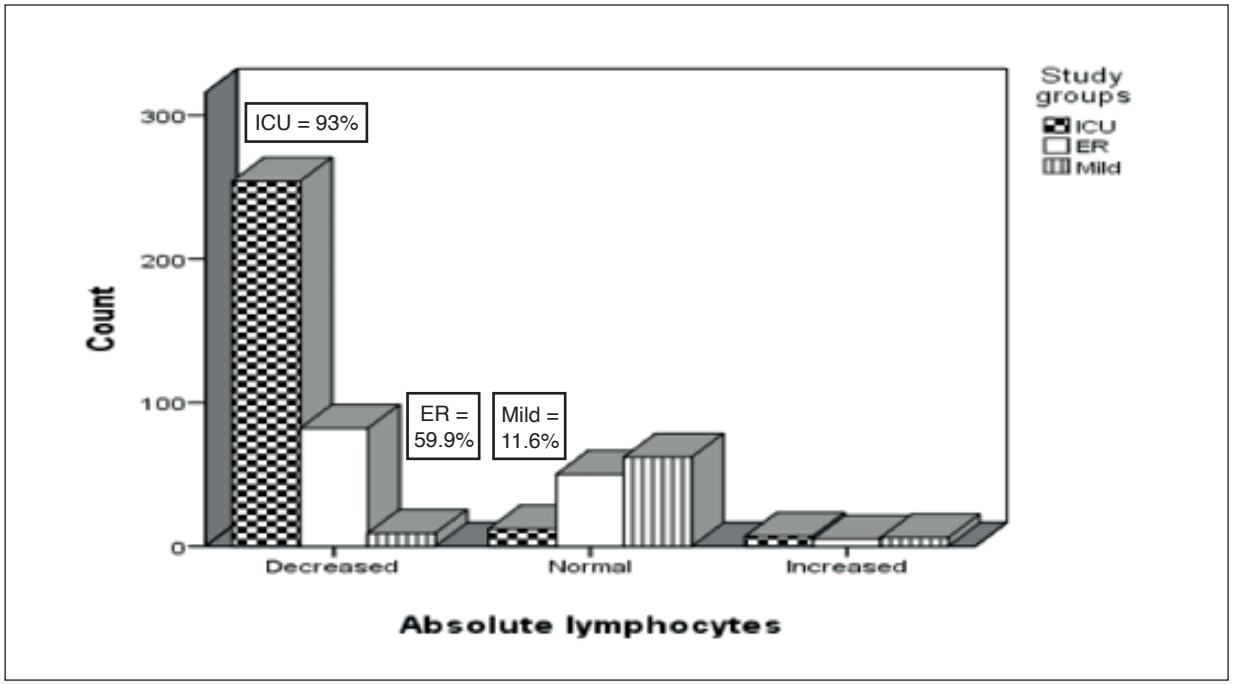

Figure 1. Distribution of Lymphocytes count among case subgroups.

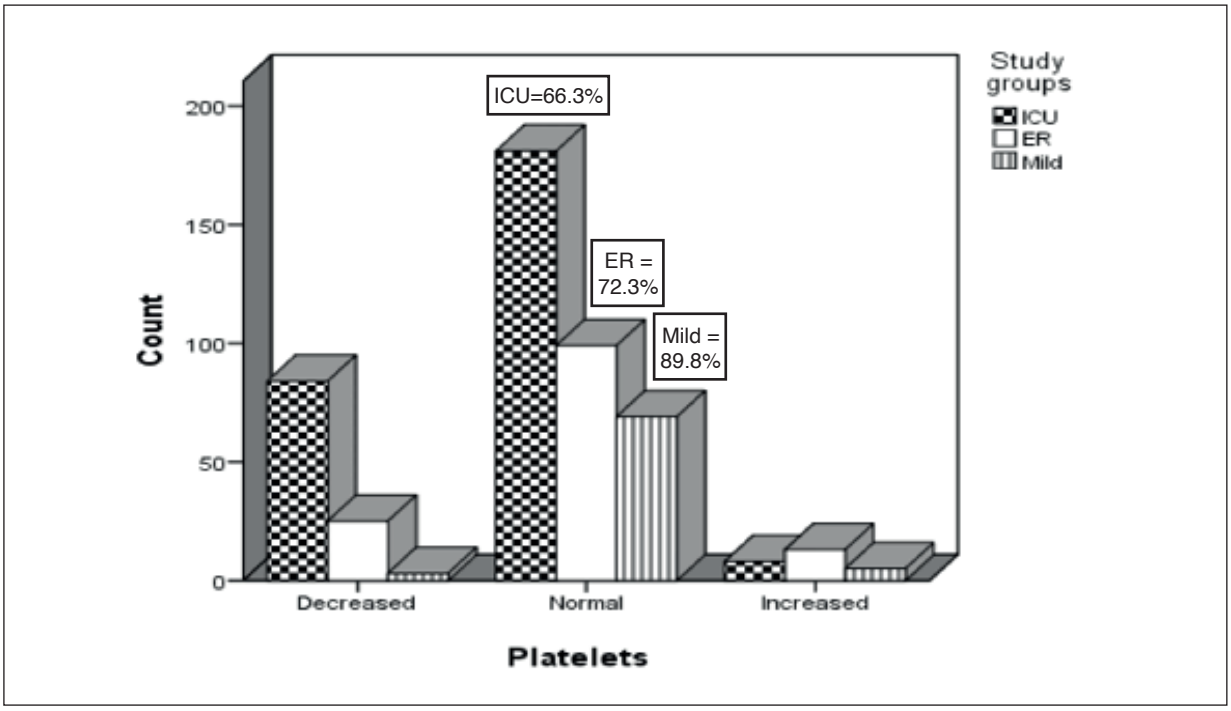

Figure 2. Distribution of PLTs count among case subgroups.

ed a significant increase in NLR and PLR between case subgroups (ICU, ER, and mild) and the control group, these results conformed to a study conducted in China showed that significant increase in PLR is associated with severe COVID-19 cases[29].

Conclusions

This study concluded that lymphopenia is associated with severe COVID-19 infection. Thrombocytopenia was associated with COVID-19 patients, mainly in the ICU. COVID-19 severity was markedly increased as NLR and PLR were markedly increased. There was an association between the patient's age and gender with the severity of COVID-19.

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Authors' Contribution

All authors worked together to complete this project. The final manuscript was read and approved by all authors.

Conflict of Interests

The authors declare that they have no conflict of interest.

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