Variations in Haematological and Immunological Parameters Among Hospitalized COVID-19 Patients

Fathia G Jaat[a]*, Mohamed Ebsaim[b], Nadia M Kermani[c], Sedik A Abokdeer[d], Ali S Arebi[e]

[a,c]Faculty of Science, Department of zoology, Zawia University-Libya

[b,e]Faculty of Medical Technology. Zawia University –Libya

[d]Libyan Medical Center- Zawia-Libya

[a]Email: f.jaat@zu.edu.ly, [b]Email: Mohamed.ebsaim@yahoo.com, [c]Email: n.kermani@zu.edu.ly, [e]Email: abokdeers71@gmail.com

Abstract

Background: Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a novel virus, has spreading globally, leading the World Health Organization to declare a pandemic. This study aims to ascertain the changes in haematological and immunological parameters in COVID-19 patients. Methods: Data from 109 confirmed COVID-19 patients admitted for treatment in the Isolation Centre at Al-Zawia city between 16 September and 29 December 2020 were retrospectively analyzed. Demographic, clinical, and laboratory data were extracted from electronic medical records and compared with those of 52 healthy controls.Results: The laboratory tests included blood routines and cellular and inflammatory biomarkers compared with healthy controls. Hospitalized patients had higher WBC (p<0.0001), platelet (*P*= 0.0060), NEU (*P*<0.0001), and RBC (*P*<0.0001) counts. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) scores were compared with the normal range where data were not available from healthy controls and the results showed significantly higher levels in patients with Covid-19 (p<0.0001). Conversely, lymphocyte (LYM) counts were significantly lower in Covid-19 patients (*P*<0.0001).   Conclusion: Complete blood count (CBC) and inflammatory biomarkers, including CRP and ESR, can help clinicians to assess the severity and prognosis of patients with COVID-19.

Keywords: COVID-2019; Complete blood count; C-reactive protein; Hospitalized.

----

* Corresponding author.

1. Introduction

Since December 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (S1ARS-CoV-2) has spread globally [1, 2]. SARS-CoV-2 infection has a wide clinical spectrum, ranging from asymptomatic infection, mild respiratory disease, and severe pneumonia with acute respiratory failure and even death [3, 4]. The most common symptoms include cough, fever, shortness of breath, weakness, malaise, and respiratory distress [3, 5]. The severity of the disease can be divided into four types based on the clinical manifestations of the patient's disease and treatment with different measures: mild, moderate, severe, and critical [6]. Patients with mild to moderate disease develop respiratory symptoms within the second week and may not require admission to hospital. Meanwhile severe and critically ill patients admitted to an intensive care unit (ICU) progress to serious complications such as shock, sepsis, and acute cardiac and kidney injury [3, 7]. According to the World Health Organization (WHO), about 80% of infected people have mild to moderate infections, 13.8% have severe infections, and 6.1% have critical illness [6]. Severe respiratory disease can be displayed in elderly and specific groups of patients with underlying medical conditions such as hypertension, chronic lung disease, diabetes, and cancer. These patients have a high risk of mortality [8, 9]. Enormous research activity across the globe has been devoted to the development of predictors of COVID-19 disease severity in an effort to rapidly determine and assess infection [10]. Laboratory biomarkers and blood tests have an important role in the early diagnosis of the current novel coronavirus pandemic. As the most routine and inexpensive laboratory procedure, blood tests have been used to provide clinicians with convenient assistance in evaluating a patient's condition [8, 11]. Analysis of the clinical characteristics of 1099 patients with COVID-19 showed abnormal parameters for lymphocytes and platelets in the peripheral blood of some patients [9]. Furthermore, complete blood counts (CBCs) present values such as white blood, neutrophil, lymphocyte and platelet counts, mean platelet volume and certain ratios of these values. The ratios of these parameters are also used as inflammatory markers [12]. C-reactive protein (CRP) is a universal inflammatory predictor which has been associated with disease development, and it is an early predictor in the diagnosis and prognosis of COVID-19[13]. Therefore, laboratory findings are essential in evaluating the condition, diagnosis and treatment of COVID-19 patients. The purpose of this study was to analyze the haematological parameters neutrophils, lymphocytes, white blood cells, platelets and immune parameters (ESR and CRP) so as to differentiate COVID-19 hospitalized patients from a control group in order to determine the predictors of severe illness.

2. Data collection

The study retrospectively enrolled 109 confirmed COVID-19 patients who were hospitalized in the Isolation Centre located in Al-Zawia city between September 16 and December 29, 2020. A total of 109 confirmed Covid-19 patients were defined as positive cases after the detection of SARS-CoV-2 RNA in oro-nasopharyngeal swab samples. Only laboratory-confirmed cases were included in this study. Also, 52 healthy controls without any chronic disease or respiratory symptoms were recruited for the control group. Demographic data and laboratory values were extracted from electronic medical records and patient files. The following variables were recorded for each patient: age, sex, diabetes, and hypertension, and laboratory assessments consisted of a complete blood count and measures of inflammatory biomarkers such as blood sedimentation ESR and CRP.

3. Statistical analysis

Statistical analyses were performed using Graph Pad Prism software Version 7. Categorical variables were described as counts and percentages, and continuous variables were described using values of median and interquartile range (IQR). Differences between the two groups were determined using the Mann-Whitney U test. Statistical significance was defined as $P < 0.05$.

4. Results

4.1 Basic characteristics of the patients

The median age of the 109 patients was 62 years (interquartile range, 71–50.5; range, 30-95 years), and 59 (45.12%) were male and 50 (45.87%) female. So men had more disease than women. In terms of coexisting disorders, diabetes was higher (N=44, 40.3%) than hypertension (N=30, 27.5%) in this group (see Table 1).

Table 1: Clinical characteristic of the 109 patients

Characteristic	Hospitalized COVID-19 patients (109)	Healthy controls (52)
Age, Median, (IQR), range, years	62 (50.5-71) 30-95	
Male sex No. (%)	59 (54.12)	10 (19.20)
Female sex No.(%)	50 (45.87)	42 (80.70)
Coexisting disorder No. (%)		
Diabetes	44 (40.3)	
Hypertension	30 (27.5)	

4.2 Blood routine and inflammatory biomarker

Table 2 presents the parameters of blood routines in patients with COVID-19 and healthy controls. Blood routine tests were conducted for all patients after admission to the Centre. The results show that patients with COVID-19 had higher white blood cell (WBC) (11.9 vs 6.95x10^3/uL; $P < 0.0001$), neutrophil (NEU) (10.6 vs 3.7x10^3/uL; $P < 0.0001$), platelets (294 vs 236.5x10^3/uL; $P = (0.0060)$ and red blood cell (4.83 vs 4.32x10^6/uL; $P<0.0001$) counts. Lymphocyte counts were significantly lower (0.9 vs 2.2x10^3/uL) in COVID-19 patients ($P<0.0001$). The concentration of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were

compared to the normal ranges since data from healthy controls were not available, and the results were significantly higher in COVID-19 patients (*P*< 0.0001).-

. **Table 2:** Laboratory findings for the 109 patients

Parameters	Reference rang	Hospitalized group Median (IQR) Total (N = 109)	Healthy controls Median (IQR) Total (N = 52)	P value
WBC x10^3/UL	4-11	11.9 (8.55-16.9)	6.95(5.75-8.32)	<0.0001
PLT x10^3/UL	150-400	294 (192-356.5)	236.5 (183.75-285)	0.0060
LYM x10^3/UL	1.5- 3	0.9 (0.6-1.35)	2.2 (1.6-2.67)	<0.0001
NEU x10^3/UL	1.5 - 5.0	10.6 (7.2-15.1)	3.7 (3.02-5.27)	<0.0001
RBC x10^6/UL	.3.80-5.80	4.83 (4.31-5.15)	4.32 (4.50-3.65)	<0.0001
CRP mg/L	0-10	124.5 (51-181.02)	NA	<0.0001
ESR mm/1h	0–15	83 (58-107)	NA	<0.0001

Data are presented as median (IQR), N is the total number of patients with available data. NA indicates that data were not available. *P* values are from Mann-Whitney U tests comparing patients and healthy controls. Differences were significant at <0.05 level

5. Discussion

The study population consisted of 59 (54.12%) male and 50 (45.87%) female patients, ranging in age from 30–95 years. Their coexisting conditions are listed in Table 1. Diabetes and hypertension represent 44 (40.3%) and 30 (27.5%) of the total respectively. In the present study, we mainly analyzed and summarized the results of the laboratory examination of samples from COVID-19 patients, especially for haematological and immunological parameters. These markers are from complete blood counts (CBCs), which are simple and inexpensive and provide several useful prognostic markers. Thus, such tests can be regularly performed by many clinicians [14]. In the current study, significantly lower lymphocyte levels were found in COVID-19 patients, which is in line with previous researches [15, 16, 17]. Liu and his colleagues also found that lymphocyte counts were decreased

in patients with ARDS compared with those without ARDS [18]. The coronavirus family of SARS-CoV, MERS-CoV and SARS-CoV-2 initiate lymphocytic depletion in infected patients and the mechanism for this may involve the direct attack of the coronavirus on lymphocytes or the immune-mediated apoptosis of lymphocytes [19, 20]. Thus, it is suggested that SARS-CoV-2 infection may affect T lymphocytes, causing a reduction in their levels and resulting to disease progression [16]. Furthermore, leukocytosis and lymphopenia have been commonly reported in COVID-19-positive patients [14]. It has been suggested that the viral particles spread through the respiratory mucosa, using the ACE2 receptor at the level of ciliated bronchial epithelial cells and then invading other cells. This will stimulate a cytokine storm in the body and triggers a series of immune responses, which lead to alterations in peripheral WBCs and immune cells such as lymphocytes [17]. The results show that white blood cell (WBC) and neutrophil (NEU) counts were significantly higher in COVID-19 patients compared with healthy controls. This finding was consistent with previous study [16]. This may be related to the cytokine storm induced by the invasion of the virus [21]. Several studies of COVID-19 have shown that patients admitted to ICU are more likely to develop neutrophilia, which is an indicator of disease progression [21, 22, 23]. The platelet counts in hospitalized patients were significantly higher compared with healthy controls. Although significant thrombocytopenia has been found in patients with severe COVID-19 infection associated with disease severity and can be used as an indicator of clinical disease deteriorating during hospitalization [20, 22, 24]. However, only around 5% of hospitalized patients and 8% of those in the intensive care unit (ICU) exhibited decreased platelet counts, perhaps due to serious infective/inflammatory conditions where endogenous and iatrogenic factors affect the count [25]. Coronaviruses may also infect bone marrow elements, resulting in abnormal haematopoiesis, or induce an auto-immune response against blood cells [26]. Increases in platelet counts have also been observed in COVID-19 disease compared to patients with severe pneumonia but without COVID-19 [14, 27]. In the current study, higher RBC levels were found in COVID-19 patients compared with the controls. This result is inconsistent with previous research which found lower RBC; thus, it is not yet fully identified whether SARS-CoV-2 affects erythrocytes [14]. Our study also found that the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) scores of COVID-19 patients were significantly higher, suggesting that these indicators represent an early warning of the effect of the progression of the disease [21, 28]. Severe illness following SARS-CoV-2 infection was associated with a higher CRP level. Increased CRP level observed in 75%-93% of sever patients [29]. Elevated CRP levels indicates the development of systemic inflammatory response syndrome (SIRS) which is accompanied by release of massive inflammatory cytokines producing a "cytokine storm" resulting to acute tissue damage, subsequent multi-systemic failure in patients with severe cases of COVID-19. Thus it can be performed to assess whether patients are developing worsening infection [30, 31]. CRP and ESR are used as clinical biomarkers for several inflammatory conditions, as their levels increase during viral infection [14, 31]. Previous studies have found statistically significant differences in ESR values between severe and non-severe COVID-19 cases, suggesting that the former are associated with elevated ESR indicating the extensive response and expression of acute-phase protein [32]. The previous study has several limitations. First, this study included a relatively small sample size. A large patients group will better represent the importance of biomarkers tests in the diagnosis of COVID19 patients. Second, some other important parameters such as coagulation parameters and other biochemical markers were not evaluated in this study, and this is the subject of future work. Finally, demographic data including clinical symptoms other comorbidities, and respiratory conditions were not included due to limited amount of data available and should

be addressed with additional study.

6. Conclusion

In conclusion, COVID-19 is a new human infectious disease caused by a novel coronavirus SARS-CoV-2 and has spread rapidly since first identified in Wuhan city and throughout China and across the world, causing varying degrees of illness. The disease is associated with abnormalities in the parameters of peripheral blood routines and inflammatory markers. Decreases in lymphocytes and increases in white blood cells, neutrophils, platelets, and red blood cells are the most obvious abnormalities. Elevated C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR) are related to the severity of the disease and aid in clinical classification. Therefore, parameters based on CBCs can be useful in predicting severity and differentiating COVID-19 patients from healthy controls.

7. Recommendations

In this study hematological and biochemical parameters are recommended at early stage of disease to investigate any alterations. This may provide useful indication for patients who require ICU care to properly control the outcomes of the pandemic.

Acknowledgements

References

[1]. C. Bao, X. Tao, W. Cui, B. Yi, T. Pan et al. 2020. SARS-CoV-2 induced thrombocytopenia as an important biomarker significantly correlated with abnormal coagulation function, increased intravascular blood clot risk and mortality in COVID-19 patients. "Experimental Hematology & Oncology" 9 (1): 1-8.

[2]. X. Xiong, G. T. Chua, S. Chi, M. Y.W. Kwan, W. H. Sang et al. 2020. A Comparison Between Chinese Children Infected with Coronavirus Disease-2019 and with Severe Acute Respiratory Syndrome 2003. "The Journal of pediatrics" 224: 30-36.

[3]. H. Esakandari, M. Nabi-Afjadi, J. Fakkari-Afjadi, N. Farahmandian, S. M. Miresmaeili. et al. 2020. A comprehensive review of COVID-19 characteristics. ."Biological procedures online" 22: 1-10.

[4]. F. Jaat, N. Kermani. 2020. Coronavirus infection: overview and immune response. "Journal of Emerging Technologies and Innovative Research" 7 (10): 3266-3269.

[5]. E. Prompetchara, C. Ketloy, T. Palaga. 2020. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. "Asian Pacific Journal of Allergy and Immunology". 38(1):1-9.

[6]. C. Wang, R. Deng, L. Gou, Z. Fu, X. Zhang, F. et al. 2020. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters "Annals of translational

medicine" 8(9):593.

[7]. M. Zhou, X. Zhang, J. Qu. 2020. Coronavirus disease 2019 (COVID-19): a clinical update. "Frontiers of medicine" 14 (2): 126-135.

[8]. E. Usul, I. Şan, B. Bekgöz, A. Şahin .2020. Role of hematological parameters in COVID-19 patients in the emergency room. ."Biomarkers in Medicine" 14(13):1207-1215.

[9]. S. Sun, X. Cai, H. Wang, G. He, Y. Lin, 2020. Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China. "Clinica chimica Acta" 507:174-180.

[10]. P. Malik, U. Patel, D. Mehta, N. Patel, R. Kelkar, 2020. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. "BMJ evidence-based medicine"111365.

[11]. L. Y. W. Lee, J. B. Cazier, T. Starkey, S. E.W. Briggs, R. Arnold. et al. 2020. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. ."The lancet oncology" 21 (10): 1309-1316.

[12]. J. Liang, S. Nong, L. Jiang, X. Chi, D. Bi, et al. 2020. Correlations of disease severity and age with hematology parameter variations in patients with COVID-19 pre- and post-treatment. "Journal of Clinical Laboratory Analysis". e23609.

[13]. G. Ponti, M. Maccaferri, C. Ruini, A. Tomasi, T. Ozben, 2020. Biomarkers associated with COVID-19 disease progression. "Critical reviews in clinical laboratory sciences" 57 (6): 389-399.

[14]. S. Kazancioglu, A. Bastug, B. O. Ozbay, N. Kemirtlek, H. Bodur, 2020. The role of haematological parameters in patients with COVID-19 and influenza virus infection. "Epidemiology & Infection" 148: e272.

[15]. R. Mardani, A. A. Vasmehjani, F. Zali, A. Gholami, S. D. M. Nasab, 2020. Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. "Archives of academic emergency medicine" 8 (1): e43

[16]. S. Lin, W. Mao, Q. Zou, S. Lu, S. Zheng. 2021. Associations between hematological parameters and disease severity in patients with SARS-CoV-2 infection. "Journal of clinical laboratory analysis" 35(1), e23604.

[17]. A. Kantri, J. Ziati, M. Khalis, A. Haoudar, K. El Aidaoui, et al. 2021. Hematological and biochemical abnormalitiesassociated with severe forms of COVID-19: A retrospective single-center study from Morocco. "PLoS ONE" 16(2) e0246295

[18]. J. Liu, Y. Liu, P. Xiang, L. Pu, H. Xiong, et al. 2020. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. "Journal of Translational Medicine" 18: 1-12.

[19]. X. Yuan, W. Huang, B. Ye, C. Chen, R. Huang, et al. 2020. Changes of hematological and immunological parameters in COVID-19 patients. "International journal of hematology". 112 (4):553-559.

[20]. D. Liao, F. Zhou, L. Luo, M. Xu, H. Wang, 2020. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. "The Lancet Haematology". 7(9):e671-e678.

[21]. D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, et al. 2020. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. "Jama" 323(11):1061-

1069.

[22]. X. Liu, R. Zhang, G. He. 2020. Hematological findings in coronavirus disease 2019: indications of progression of disease. "Annals of hematology" 99 (7):1421-1428.

[23]. J. Liu, Y. Liu, P. Xiang, L. Pu, H. Xiong, C. Li. 2020. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. "Journal of Translational Medicine" 18: 1-12.

[24]. G. Ponti, M. Maccaferri, C. Ruini, A. Tomasi, T. Ozben. 2020. Biomarkers associated with COVID-19 disease progression. "Critical reviews in clinical laboratory sciences" 57(6): 389-399.

[25]. A. Rampotas, S. Pavord. 2020. Platelet aggregates, a marker of severe COVID-19 disease. "Journal of Clinical Pathology" 16, 206933.

[26]. M. Yang, M.H.L. Ng, C. K. Li. 2005. Thrombocytopenia in patients with severe acute respiratory syndrome (review) "Hematology". 10:101–105

[27]. S. Yin, M. Huang, D. Li, N. Tang. 2020. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARSCoV2. "Journal of thrombosis and thrombolysis" 1- 4.

[28]. A. Jin, B. Yan, W. Hua, D. Feng, B. Xu. 2020. Clinical characteristics of patients diagnosed with COVID-19 in Beijing. "Biosafety and Health" 2(2): 104-111.

[29]. J. L. Frater, G. Zini, G. d'Onofrio, H. J. Rogers, J. L. Frater, 2020. COVID- 19 and the clinical hematology laboratory. "International journal of laboratory hematology" 42: 11-18.

[30]. Q. Li, X. Ding, G. Xia, H. G. Chen, F. Chen, 2020. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: A retrospective case-control study. "EClinicalMedicine" 3 (23):100375.

[31]. B. M. Henry, M. H. S. de Oliveira, S. Benoi, M. Plebani, G. Lippi .2020. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. "Clinical Chemistry and Laboratory Medicine" 58(7): 1021-1028.

[32]. Lapić I, Rogić D, Plebani M. Erythrocyte sedimentation rate is associated with severe coronavirus disease 2019 (COVID-19): a pooled analysis. "Clinical Chemistry and Laboratory Medicine" 58(7):1146-1148