ORIGINAL RESEARCH

Haematological Traits in Symptomatic and Asymptomatic COVID-19 Positive Patients for Predicting Severity and Hospitalization

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Objective: The present investigation aims on the clinical attributes and haematological parameters between symptomatic (COVID–19 ICU) and asymptomatic (COVID–19 homes isolation) patients as predisposing sign for COVID-19 related mortality.

Materials and Methods: A retrospective cohort research was conducted of admitted patients to ICU, who were suffering from severe COVID-19 in Aseer Central Hospital, Abha, Kingdom of Saudi Arabia (KSA) from July 2020 until September 2020. The study included individuals with COVID −19 and ICU admission as symptomatic group and others who are COVID–19 positives with quarantine as asymptomatic group. Epidemiological, clinical and haematological laboratory data were retrospectively collected, analysed with control subjects.

Results: Of the 38 ICU patients studied, the most common symptoms were fever and respiratory distress (100%), cough (86.8%). Majority were of Saudi origin (78.9%). Eighteen (47.4%) COVID-19 ICU patients showed leukocytosis, 6 (15.8%) had severe thrombocytopenia (with most having thrombocytopenia), 18 (47.4%) were anaemic. A significant correlation was observed between the WBC, RBC, Hb, platelets, neutrophil and lymphocyte count between ICU inmates compared with quarantine (p < 0.001) and RBC, Hb, neutrophil and lymphocyte count with control groups (p < 0.001).

Conclusion: From the observations it is evident that, the blood tests have potential clinical value in predicting COVID-19 progression. Further, patient characteristics including age, leukocyte count, RBC, platelets and differential leukocyte counts may be significant predictors for monitoring the progression of the critical illness observed in SARS-COV-2 patients. Also, treatment procedures can be re-defined further to reduce COVID–19 mortalities in more critically ill COVID-19 individuals.

Keywords: COVID-19, blood test, ICU, quarantine, leukocyte count, erythrocyte count, platelet count

Introduction

A pandemic of coronavirus disease 2019 (COVID-19) is a viral infection which cause severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a variety of disease presentation and severity.[1] COVID-19 has affected almost the whole world, with death of approximately more than 6.2 million worldwide and 500 million cases, since that fateful December month of 2019, and more than 9000 deaths and more than 7.5 lakh cases have been recorded in KSA.[2] Epidemiological researches have depicted that 6–10% of COVID-19 affected patients progress to a more critical stage and will be in dire need of admittance to the intensive care unit (ICU) on account of acute respiratory.[3] Invasive ventilation is usually required by most of these ICU admitted patients, due mostly to intensive lung injury and acute respiratory distress syndrome (ARDS).[4] Till now, most of these patients on invasive mechanical ventilation (MV) have

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depicted an increased mortality pattern.[5] Most ICU harbouring these COVID-19 patients have shown a mortality rate of 50–65% range.[6–8] Some ICU keeping COVID-19 patients on MV have reported a mortality rate as high as 97%.[9]

Many studies have shown a significant alteration in blood investigations associated with SARS-CoV-2 as well as the disease outcomes.[10–13] In addition, very few studies provide correlation between peripheral blood WBC morphologic changes and disease outcomes.[14] Another study demonstrated the quantitative and qualitative of the peripheral blood changes in COVID-19 cases which showed reduction in T cell count.[15]

In many studies, COVID-19 has shown a link with inflammation and thrombosis. It has been shown that serious cases had thrombotic complications in ICU COVID-19 patients. Another study showed the association between C-reactive protein (CRP) and infection with COVID-19.[16,17] As platelets are critical in haemostasis, thrombosis, and inflammatory responses, one study showed that COVID-19 may induce production of autoantibodies which leads to destruction of platelets by immune responses which was approved in another study in patients infected with human immunodeficiency virus (HIV).[18] It is well known that during infection, the platelets are activated and adhered to the sub-endothelium, their hyperactivity leads to thrombosis, arterial ischemia and in many cases causes pulmonary embolisms. Many viral infections such as HIV, hepatitis C virus (HCV) and influenza virus can directly lead to hyperactivity of the platelets.[19–22] In a recent study COVID-19 has been found to induce hyperactivity of the platelets through binding of spike protein to ACE2 receptor. It has been approved that SARS-CoV-2 can induce platelet activation which may contribute in thrombus formation and inflammatory responses in COVID-19 patients.[23] One of the important inflammatory markers, which give an insight to the inflammation going on in various organs is the Platelet lymphocyte ratio (PLR).[24,25] Some studies have also found it to be independent from either platelet count or lymphocyte count.[25]

Fast and correct laboratory diagnosis of active COVID-19 infection is one of the keystones of pandemic control. If these COVID-19 serious cases can be identified early by haematological and other parameters, it can facilitate clinicians to take early appropriate remedial measures to control the morbidity and mortality of COVID-19 cases.[26] Some earlier literature on reporting on laboratory-confirmed COVID-19 cases have noticed changes in the haematological parameters, which included neutrophil count and lymphocyte count.[27,28] With a view of the above, we undertook this particular research to further clarify the clinical attributes and haematological parameters in ICU admitted COVID-19 patients compared to COVID-19 positive patients without symptoms and healthy controls.

Materials and Methods
Study Design and Setting
A retrospective cohort study was conducted at Aseer Central Hospital, Abha, the largest government hospital in Abha, Aseer province. All critical care admissions from October to December 2020 presenting to any of the intensive care units of the hospital were included in the research. All selected ICU critically ill participants and quarantine individuals had established severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection which was earlier confirmed by positive report on polymerase chain reaction (PCR) investigation of a sample from nasopharynx or aspirate from trachea. The patients who were included in the present study had their clinical outcomes monitored until February 2021, the last date of the research follow-up.

Study Participants
Thirty-eight patients aged sixteen years to eighty-three years, admitted to the ICU with COVID-19 were included in this study. Laboratory confirmation that the patients were SARS-CoV-2 infected was based on positive reverse-transcriptase-polymerase chain-reaction (RT-PCR) assay.[29] They were designated as group-1. Those were compared with twenty-nine COVID-19 quarantined patients who were designated as group-2 and twenty healthy individuals who have not been infected by COVID-19 as group-3.

Exclusion and Inclusion Criteria

Exclusion criteria included previously known participants having coagulopathy, pregnancy, antiplatelet therapy, current use of systemic anticoagulants, vitamin K antagonists and patients who presented with serious cardiac problems. Quarantined patients, who fitted the criteria, were randomly selected from records.

Ethical Consent

Our study complies with the Declaration of Helsinki. Ethical approval has been provided from Regional Committee for Research Ethics [No of Registration (H-06-8-091)] vide REC-NO: REC-03-09-2020, Ministry of Health, Directorate Health Affairs - Aseer Region, KSA. Informed consent was obtained from each study participant after describing the objective and procedures of the study. Every response of the participants was kept confidential.

Detection of COVID-19 by Real Time-PCR and the Conditions of the Test

A nasopharynx samples were collected from assigned groups and proceeded for DNA and RNA extraction using magna pure DNA and viral NA kit (Roche). The extracted samples were amplified by the RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Altona diagnostic), to detect S gene for SARS-CoV-2 and E gene for B-βCoV. For quality control check, positive control contains both targets, B-βCoV and SARS-CoV-2 and negative controls (H2O) were used per test. After that, samples were analysed by Light Cycler 480 II (LC480II, Roche) and performed according to the manufacturer's instructions. Samples with a CT value below 35 were considered positive amplification of the SARS-CoV-2 S gene.

Data Collection

All study data were retrieved from ICU records after proper permission. Collected clinical variables included demographics, comorbidities, and haematological parameters after ICU admission.

Retrospective Laboratory Data Analysis

All data were collected from the patient records after adequate permission and then entered in IBM SPSS version 23 [IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 22.0. Armonk, New York, USA] for further analysis. The data were subjected to general analysis like mean, standard deviation, standard error, kurtosis, skewness, etc, and then comparison was done with the help of non-parametric test, ie, Mann–Whitney test where p-value (2-tailed), Wilcoxon W, Mann–Whitney U, etc were analysed. PLR was calculated by dividing the platelet count by the lymphocytes.

Results

ICU patients had a mean±SD of $15.11 \pm 11.612 \times 10^9$/L for WBC, with a minimum of 2.15×10^9/L and maximum of 47.49×10^9/L (Table 1). RBC count was 4.11 ± 1.26 million cells per mcL with a minimum of 2.38 million cells per mcL and maximum of 8.12 million cells per mcL. The Hb was 11.30 ± 3.12 g/L, with minimum being 6.00 g/L and maximum being 20.80g/L. Platelets' mean±SD was $184.95 \pm 123.3 \times 10^9$/L, with a minimum of 18.00×10^9/L and 553.00×10^9/L maximum. Neutrophil count was (mean±SD) $13.34 \pm 11.38 \times 10^9$/L with a minimum of 0.50×10^9/L and a maximum of 43.80×10^9 /L. Lymphocyte count had a mean±SD of $0.97 \pm 0.66 \times 10^9$/L, the minimum being 0 and maximum being 2.78×10^9/L. In the case of monocytes, it (mean±SD) was $0.63 \pm 0.46 \times 10^9$/L, with a minimum of 0.10×10^9/L and a maximum of 1.97×10^9/L. The Eosinophil count had a mean±SD of $0.12 \pm 0.23 \times 10^9$/L with minimum being 0 and maximum of 0.97×10^9/L. Basophils were in the range of $0.039 \pm 0.04 \times 10^9$/L (mean±SD) with maximum of 0.19×10^9/L and minimum of 0 (Table 1). PLR was 189.895.

Quarantined group had a mean±SD of $5.7 \pm 0.48 \times 10^9$/L for WBC of with a minimum of 2.18×10^9/L and maximum of 14.92×10^9/L (Table 1). RBC count was 5.79 ± 0.55 million cells per mcL with a minimum of 4.87 million cells per mcL and maximum of 6.83 million cells per mcL. The Hb was 16.0 ± 1.97 g/L, with minimum being 8.20 g/L and maximum being 20.20 g/L. Platelets' mean±SD was $306.76 \pm 106.77 \times 10^9$/L, with a minimum of 156.00×10^9/L and 567×10^9/L maximum. Neutrophil count was (mean±SD) $2.54 \pm 1.96 \times 10^9$/L with a minimum of 0.66×10^9/L and a maximum of 10.94×10^9/L. Lymphocyte count had a mean±SD of $2.519 \pm 0.82 \times 10^9$/L, the minimum being 0.88 and maximum being 4.26×10^9/L. In the

Table 1 Characteristics of the Blood Parameters of ICU Patients with COVID-19, Quarantine Patients with COVID-19

Parameters	Normal Range	Mean±SD		
		ICU (n=38)	Quarantine (n=29)	Control (n=20)
WBC × 10⁹/L	4.5–11	15.11±11.612	5.7±0.48	6.53+1.96
RBC × million cells per microliter (mcL)	4.5–11	4.11±1.26	5.79±0.55	5.31±0.31
Hgb, g/L	11.5–15.0	11.30±3.12	16.0±1.97	15.5+1.18
Platelets × 10⁹/L	150–450	184.95±123.3	306.76±106.77	286.65+86.54
Neutrophil count, × 10⁹/L	2.0–8.0	13.34±11.38	2.54±1.96	3.22+1.32
Lymphocyte count, × 10⁹/L	1.5–3.5	0.97±0.66	2.519±0.82	2.54+0.785
Monocyte count, × 10⁹/L	0.2–0.8	0.63±0.46	0.49±0.21	0.53+0.126
Eosinophil count, × 10⁹/L	0.04–0.4	0.12±0.23	0.15±0.174	0.22+0.178
Basophil count, × 10⁹ /L	0.01–0.1	0.039±0.04	0.04±0.022	0.039+0.0236
Platelet to lymphocyte ratio	36.63–172.68	189.895	121.746	112.766

case of monocytes, the mean±SD was $0.49\pm0.21\times10^9$/L, with a minimum of 0.14×10^9/L and a maximum of 1.12×10^9/L. The Eosinophil count had a mean±SD of $0.15\pm0.174\times10^9$/L with minimum being 0 and maximum of 0.79×10^9/L. Basophils were in the range of $0.04\pm0.022\times10^9$/L (mean±SD) with maximum of 0.08×10^9/L and minimum of 0 (Table 1). PLR was 121.746.

Considering WBC, the mean±SD for the control group was $6.53+1.96\times109$/L with a minimum of 3.58×109/L and maximum of 11.65×109/L (Table 1). RBC count was 5.31 ± 0.31 million cells per mcL with a minimum of 4.62 million cells per mcL and maximum of 5.98 million cells per mcL. Hb level was $15.5+1.18$g/L, with minimum being 12.70g/L and maximum being 17.60g/L. The mean±SD for Platelets was $286.65+86.54\times109$/L, with a minimum of 156×109/L and 546×109/L maximum. Considering neutrophil count, it was (mean±SD) $3.2+1.32\times109$/L with a minimum of 1.56×109/L and a maximum of 6.56×109/L. The mean±SD for lymphocyte count was of $2.54+0.785\times109$/L, the minimum being 1.34 and maximum being 4.94×109/L. In the case of monocytes, the mean±SD was $0.53+0.126\times109$/L, with a minimum of 0.37×109/L and a maximum of 0.9×109/L. The Eosinophil count had a mean±SD of $0.22+0.178\times109$/L with minimum being 0.07 and maximum of 0.76×109/L. Basophils were in the range of $0.039+0.0236\times109$/L (mean±SD) with maximum of 0.09×109/L and minimum of 0.09 (Table 1). PLR was found to be 112.766.

A significant correlation was seen between the RBC (Figure 1), Hb (Figure 2), Neutrophil count (Figure 3) and Lymphocyte count (Figure 4) count ($p < 0.001$) of ICU patients with COVID-19 and healthy controls. However, no such correlation was seen between Monocyte count (Figure 5), Eosinophil count (Figure 6) and Basophil (Figure 7) count ($p = 0.294$, $p = 0.116$ and $p = 0.996$).

It was seen that there is a significant correlation between the WBC (Figure 8), RBC (Figure 1), Hgb (Figure 2), Platelets (Figure 9), Neutrophil count (Figure 3) and Lymphocyte count (Figure 4) of the ICU patients with COVID-19 and Quarantined patients with COVID-19 ($p < 0.001$). But no such relationship was seen between Monocyte (Figure 5) count ($p = 0.617$), Eosinophil (Figure 6) count ($p = 0.005$) and Basophil (Figure 7) count ($p = 0.613$) (Table 1).

It was noticed that no significant correlation existed between COVID-19 cases from quarantine with healthy participants in WBC (Figure 8) count ($p = 0.154$), Hgb (Figure 2) ($p = 0.108$,) (Figure 9), (Figure 3), Lymphocyte count (Figure 4) ($p = 0.831$), Monocyte count (Figure 5) ($p = 0.476$), Eosinophil count (Figure 6) ($p = 0.041$), Basophil count (Figure 7) ($p = 0.648$). However, significant correlations occurred between platelets (Figure 9) and neutrophil count (Figure 3) ($p<0.001$).

Discussion

The virus responsible for COVID-19 is mutating so rapidly that we are unable to understand the different speculations that its effects are having on the human body. Nonetheless, the haematological and biochemical parameters are still to be elucidated perfectly, so that future generations can control the mutated virus in the human body. Therefore, we abridged a comparative scrutiny of haematological attributes of 38 ICU COVID-19 patients, 29 quarantined COVID-19 patients and 20 controls.
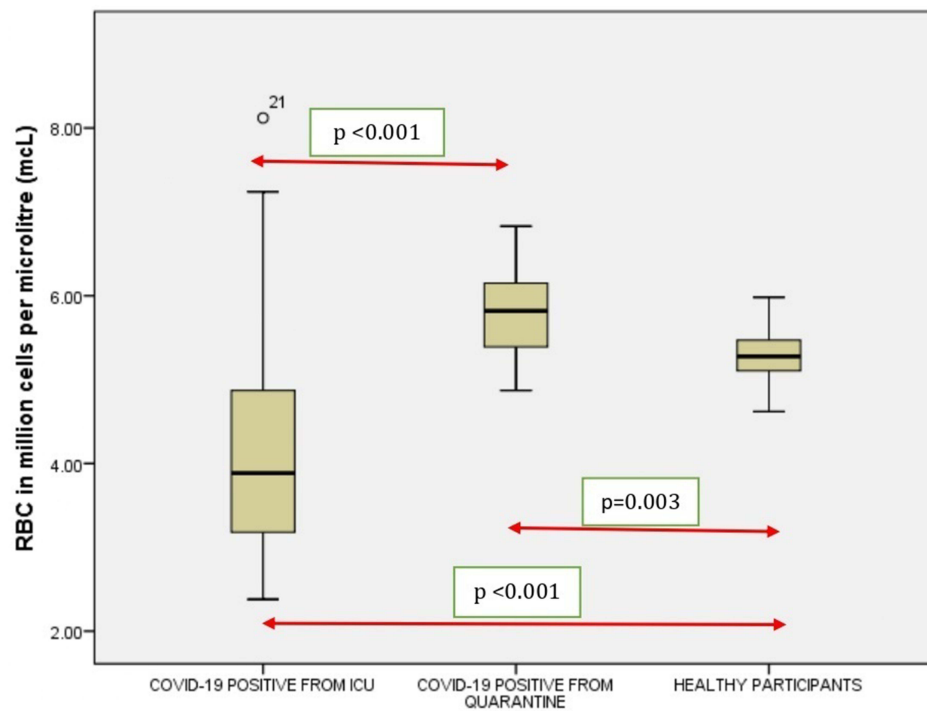
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Figure 1 Comparison of RBC count in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers).
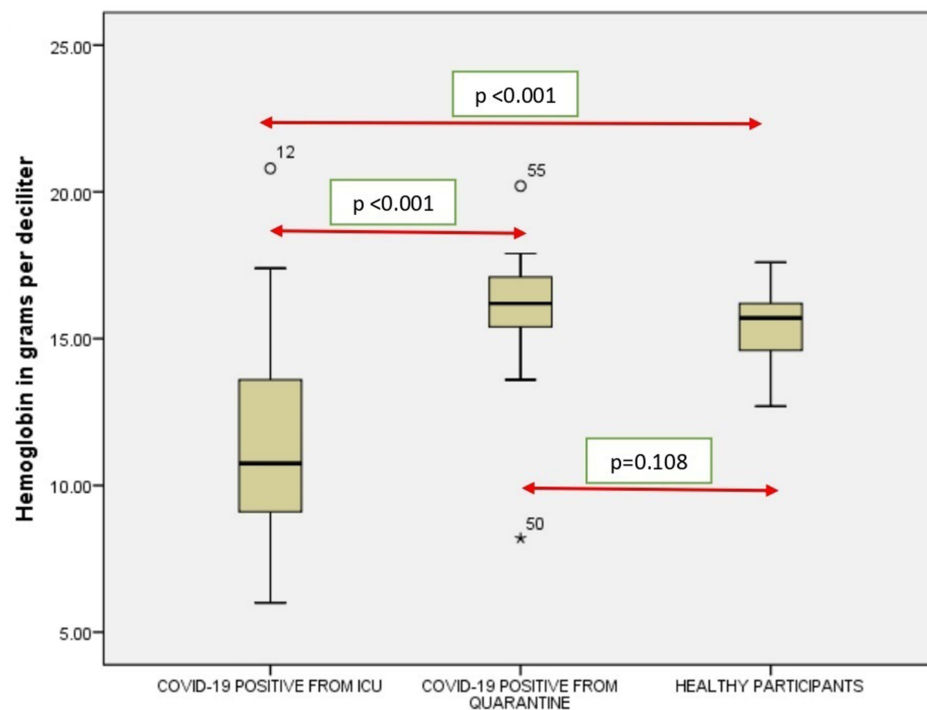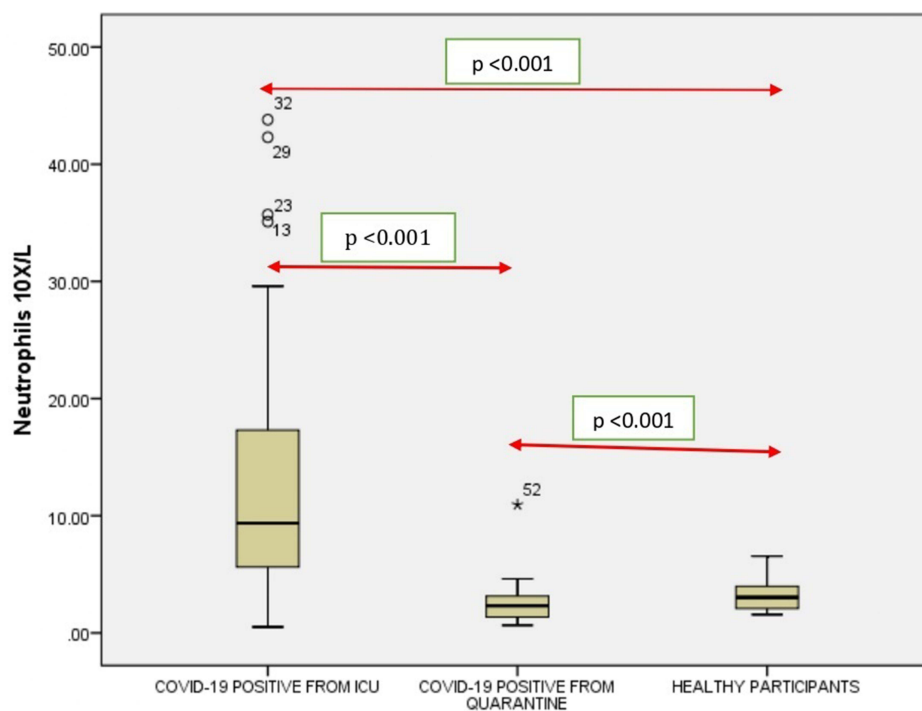

Figure 2 Comparison of hemoglobin in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers). *The asterisk is used for higher observed data points outside the boundary of the whiskers.
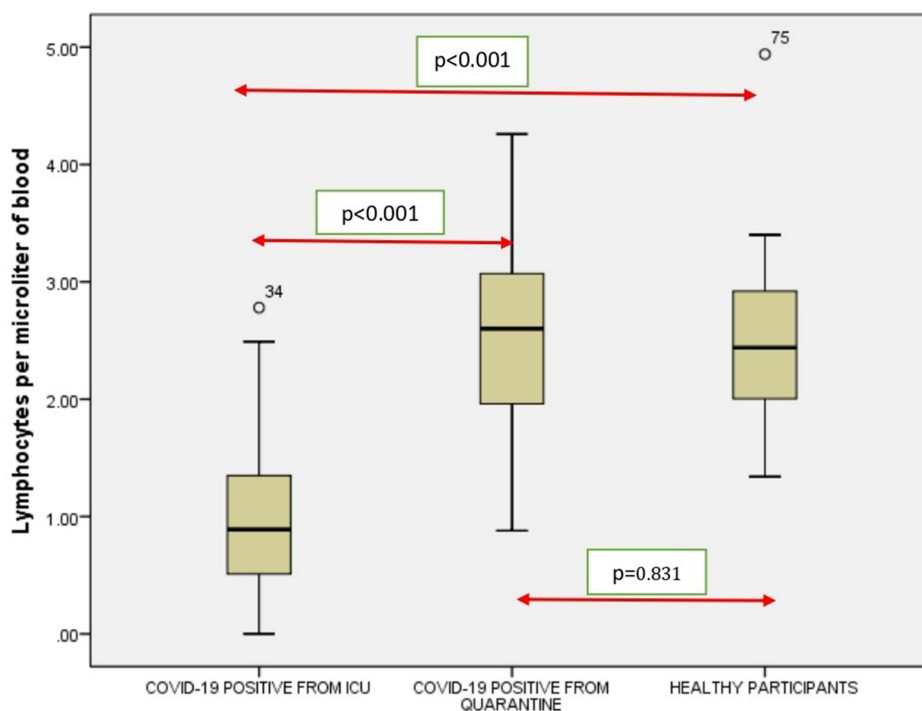
Figure 3 Comparison of neutrophils in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points out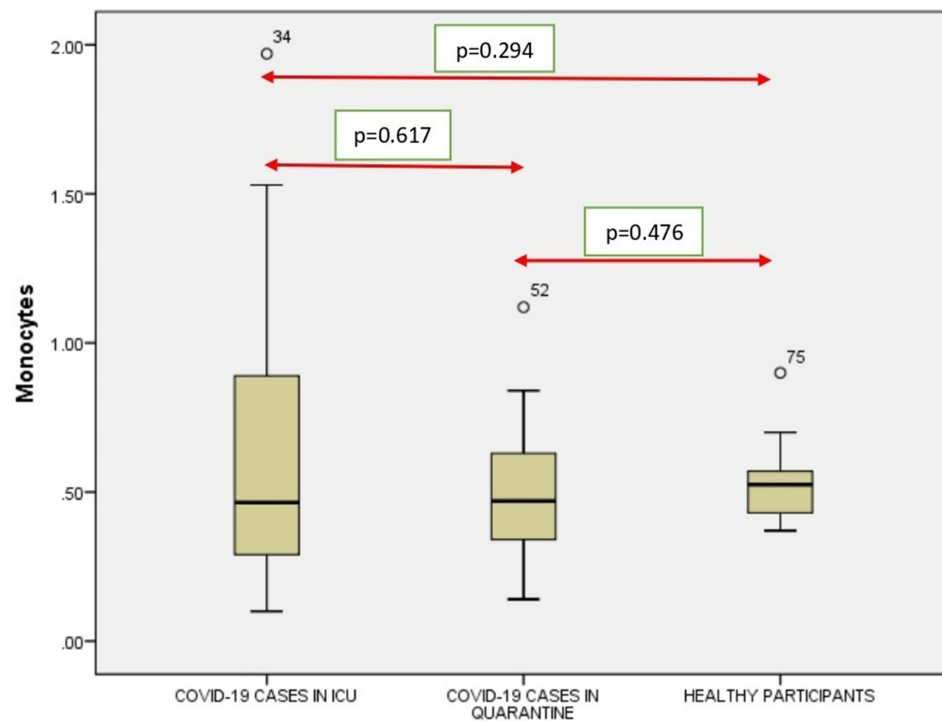side the boundary of the whiskers). *The asterisk is used for higher observed data points outside the boundary of the whiskers.

Figure 4 Comparison of lymphocytes in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers).
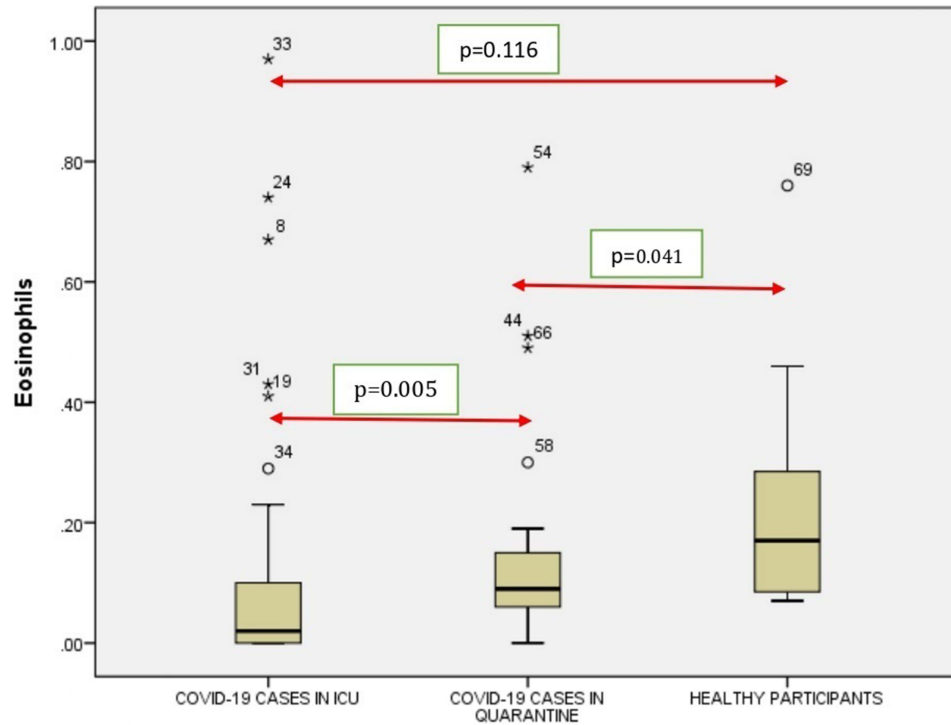
Figure 5 Comparison of monocytes in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers).

Figure 6 Comparison of eosinophils in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers). *The asterisk is used for higher observed data points outside the boundary of the whiskers.
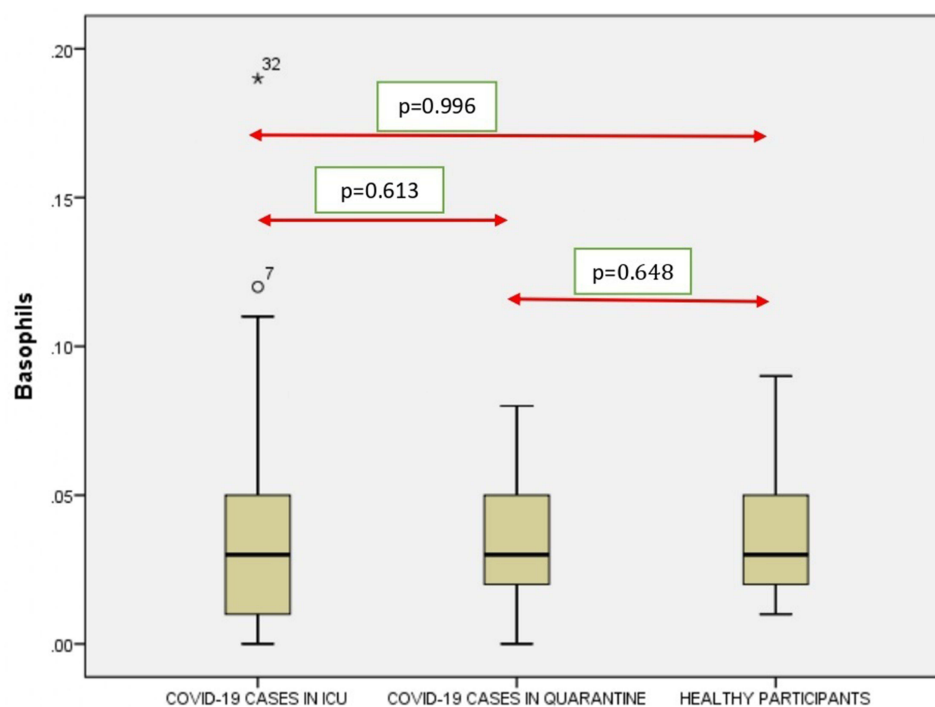
Figure 7 Comparison of basophils in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers). *The asterisk is used for higher observed data points outside the boundary of the whiskers.
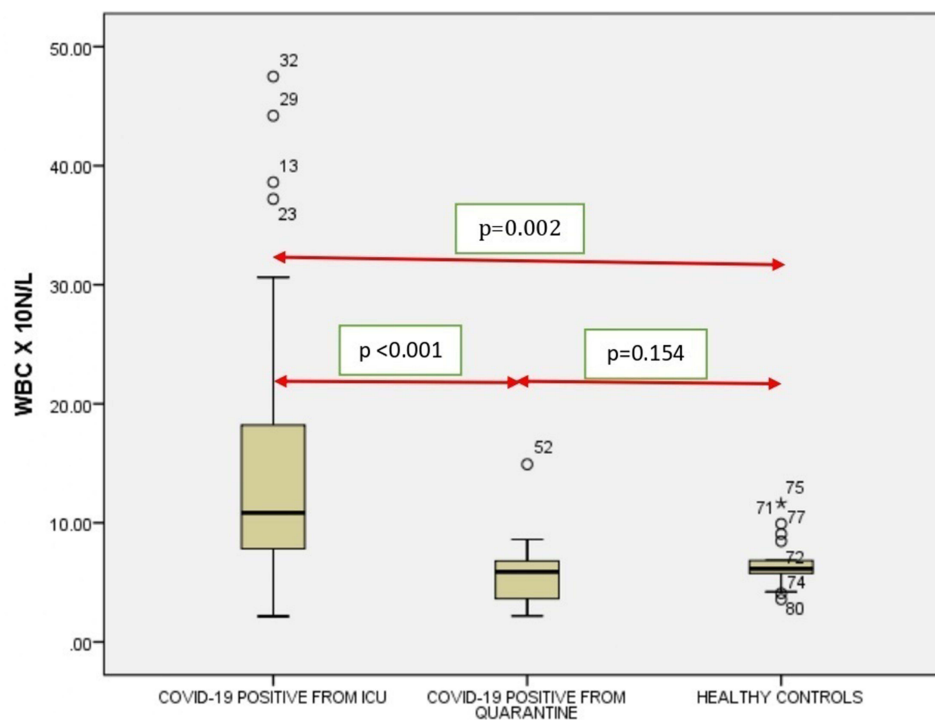

Figure 8 Comparison of WBC count in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers). *The asterisk is used for higher observed data points outside the boundary of the whiskers.
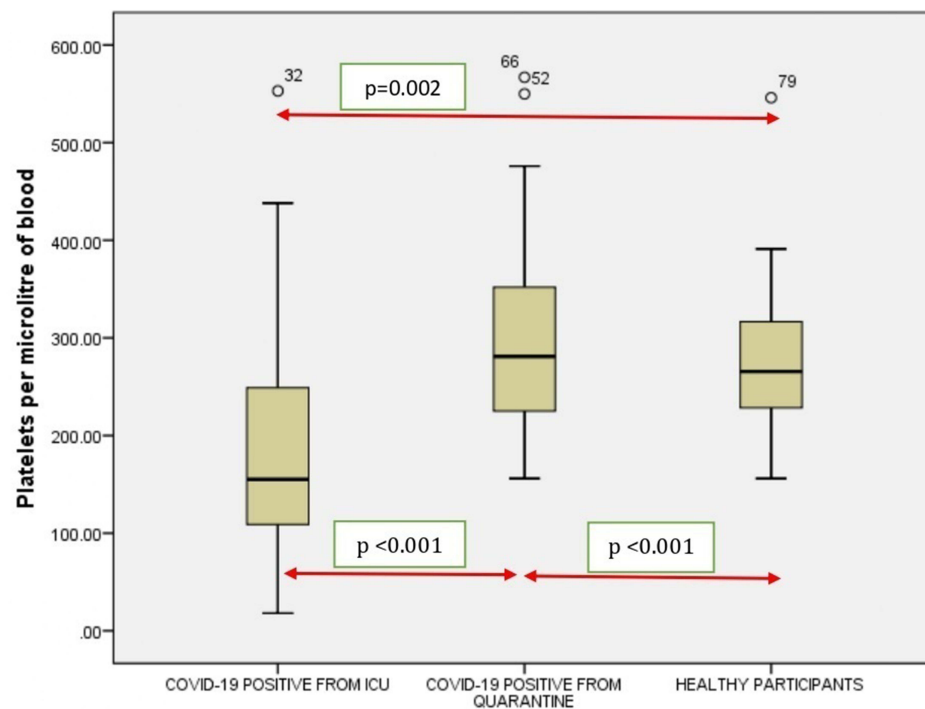
Figure 9 Comparison of Platelets in COVID-19 positive cases of ICU patients, quarantined patients with COVID-19 and healthy participants. Red double direction arrow: used to compare the *p* value between various groups. °Outlier (observed data points outside the boundary of the whiskers).

Leukocytosis, low RBCs (compared to quarantined subjects and controls), low haemoglobin (compared to quarantined subjects and controls), decreased platelets (compared to quarantined subjects and controls), neutrophilic leukocytosis, lymphocytopenia were some of the prominent features of our study. In Chongqing (China), the common symptoms that were observed were cough, fatigue, fever and expectoration; these symptoms were also observed in many other studies.[30–33] But some major symptoms like myalgia, fever, malaise and chills were also reported[34] and common symptoms like chest pain and dyspnoea were also reported.[35]

The haematological disorders observed in critically ill COVID-19 patients are complex and multifactorial. In this study of 38 individuals with COVID-19 hospitalized in the ICU of Aseer Hospital, it was seen that significant correlation was seen between the RBC, Hb, Neutrophil count and Lymphocyte count ($p < 0.001$) of ICU patients with COVID-19 and healthy controls. It was noticed that abnormal hematologic parameters (including lymphocytopenia, neutrophilia and eosinopenia) and declining kidney functions were correlated with a greater peril of alarming hospital itinerary. Many previous researches have depicted that approximately 5% of SARS-CoV-2 patients become grievously sick, evolving organ malfunctions and ultimately failure.[36] Recently, a study has depicted irreversible damage caused to the erythrocyte proteome by COVID-19.[37] Reactive oxygen species plays a vital role in leading to the damage of the RBCs, memorialize the neutrophil activation. SARS-CoV-2 attacking facilitates iron removal from the heme prosthetic group, which leads to the loss of functional haemoglobin.[38,39] The authors found that oxidative stress connected with COVID-19 damages essential proteins in erythrocytes, including those that influence membrane structure and the ability to transport and deliver oxygen. Because mature erythrocytes cannot synthesize new proteins to replace damaged ones and the average lifespan of erythrocytes is 120 days, the authors hypothesize that the circulation of irreversibly damaged erythrocytes with impaired function could contribute to the long-term effects of COVID-19.[25] The mechanism behind the lymphopenia in ICU patients might be due to the direct attack by the virus in the lymphocytes or the mechanism might be one of immune-mediated apoptosis of lymphocytes.[40–42] The research shows that the median age of the ICU patients was 55.5 years while the median age of the quarantined patients was

25 years; this is same as some previous studies which showed that the median age of the patients who were in quarantined with COVID-19 was lower than the ICU cohort.[43,44] It is a renowned fact that the aged people greater number of limited organ function, comorbidities, biological aging, impaired immune system and more serious complications, which were pointed out by earlier studies on aged people afflicted with COVID-19[45,46] hence it is of utmost importance that clinicians should treat them as a high-risk group.

Differential count (Neutrophil, eosinophil, etc) showed some remarkable differences from the normal in both ICU and COVID-19 positive cases, which also correlated with previous studies. All these add to the remarkable distinction, which can be pursued in future studies.[47–49]

An essential pathogenetic mechanism in COVID-19 which leads to kidney and lung injury is endothelial injury.[50–52] Comparison of haematological findings showed that the RBC, Hb, Neutrophil count and Lymphocyte count ($p < 0.001$) of ICU patients had significant differences with healthy controls. Materializing evidence hints that neutrophil, and the imbalance between neutrophil extracellular trap (NET) which plays a key role in the pathophysiology of coagulopathy, inflammation, organ damage, and also immunothrombosis, mainly is responsible for the characteristics of severe cases of COVID-19.[53] This also mostly matches earlier research done on patients with COVID-19.[54,55] Damage to the endothelium leads to recruitment of perivascular T-cells and distorts the alveolar capillary barricade in the lungs.[56] Acutely damaged endothelium in COVID-19 is correlated with structurally distorted capillaries and further evidence of compensatory neovascularisation.[57] This lower than is desirable endothelial barricade provokes oedema of the lungs, and subsequent proteinuria, which are commonly seen in patients afflicted with severe kidney and lung diseases.[58,59] As abundant NETs are found in the circulation and in kidney and lung tissues of patients afflicted with COVID-19,[60] their stockpiling delineates a key provocation to generate renal and pulmonary microvascular thrombosis, which ultimately leads to COVID-19-related organ failure.[61,62] A nonspecific inflammatory marker, the PLR, implies concurrent interaction between platelet count and lymphocyte count, reflects aggregation, as well as inflammatory pathways. In many cases, it has been found to be elevated in response to many acute as well as chronic proinflammatory conditions. Our study had elevated PLR in ICU, compared to healthy controls[25,63–65] and has reported a strong correlation between elevated PLR and mortality in Covid-19 patients like some other studies.

Limitations of the Study

We have to admit that the study has many limitations. First, retrospective cross-sectional research furnishes no features and details on a cause to effect relationship. Secondly, the findings have been hampered by the limited number of haematological parameters studied. Another drawback that we faced was that we were not able to perfectly match the study participants as required. Also, some more parameters were not done, and we were not able to include them in our study. Since this was a retrospective cohort study, it was impossible to follow timing of blood count. Also, another drawback was the number of patients in ICU who died; we were unable to get the data due to technical issues. Further exploration of these markers is required for utilization for risk stratification in patients afflicted with COVID-19. By doing research in a larger number of COVID-19 cases combined with COVID-19 autopsy information will surely help us to get more accurate information on the clinical characteristics and their contribution in managing the disease. This will additionally assist in formulating a vigorous scheme to dominate and attenuate the COVID-19 pandemic at large.

Conclusion

We have seen in this research that characteristics of ICU patients, including age, leukocyte count, platelet count, RBC count and differential leukocyte count may be noteworthy futuristic for developing managing plans for critically ill SARS-COV-2 afflicted patients. These alterations in the said parameters have shown that patients having severe COVID-19 disease could be treated beforehand with the said alterations, and thus these may also serve as a possible biomarker for those people who needs hospitalization and ICU care. Also, close monitoring of platelets should be done to prevent clotting in ICU patients. Also, it was seen that PLR determination was useful in COVID-19 for determination of the health peril. However, further evaluation of these parameters is needed to be utilized for peril stratification purposes. COVID-19 is very unpredictable, since it is mutating constantly in defined periods, which leads to variety in the clinical

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symptoms and signs. This is the main reason that high-risk patients need constant and strict monitoring and timely supportive measures and adequate treatment.

Data Sharing Statement

The datasets used in this study are available from the corresponding author upon request.

Acknowledgment

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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