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Original Article

Preliminary Study of sCD14 and sCD163 as Predictors of Disease Severity and ICU Admission in COVID-19: Relation to Hematological Parameters, Blood Morphological Changes and Inflammatory Biomarkers

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Abstract. ***Background and Objectives:*** **Research supports the role of monocyte/macrophage activation in COVID-19 immunopathology. This study aimed to evaluate sCD14 and sCD163 - the monocyte activation markers - and to investigate their relation to hematological parameters and blood morphology in COVID-19 infection.**
Methods**: This is a case-control study that included 70 COVID-19 patients. Patients were subdivided into two groups: 23 severely diseased ICU-admitted patients and another group of 47 non-ICU-admitted patients. sCD163 and sCD14 levels were determined using ELISA.**
Results**: sCD163 and sCD14 showed significantly higher levels in sera of patients compared to the control group, with significantly higher levels of sCD163 in ICU-admitted patients than non-ICU admitted patients. Receiver operating characteristic curve analysis demonstrated the usefulness of sCD163 with a cut-off value of 734 ng/mL as a potential marker to discriminate between ICU and non-ICU admitted COVID-19 patients (sensitivity of 81.16%; specificity of 96.67% and positive predictive value of 98% with area under the curve of 0.930). sCD163 levels showed a positive correlation with total white blood cells, absolute neutrophilic count, Neutrophil/Lymphocyte ratio, and a negative correlation with platelet count. sCD14 levels positively correlated with D-dimer values associated with a shift to the left and neutrophilic toxic granulations in blood morphology.**
Conclusion**: High sCD163 and sCD14 levels, hematological parameters, and blood morphology reflect monocyte activation in COVID-19 infection. sCD163 is a potential marker of disease severity. These findings support further study of therapeutics targeting macrophage activity in COVID-19 patients with high sCD163 levels.**

Keywords: COVID-19; sCD14; sCD163; Blood count; Blood morphology.

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Introduction. The coronavirus disease of 2019 (COVID-19) infection has resulted in 4.8 million cases and 323,000 deaths worldwide[1-3] until May 2020. At present (August 2023), WHO shows 768.983.095

confirmed cases and 6.953.743 deaths (https://covid19.who.int/)

Monocytes and macrophages have been implicated in the pathogenesis of COVID-19 infection, as evidenced by the detection of infiltration of monocyte-derived macrophages in affected lungs of severely diseased COVID-19 patients.[4,5]

CD14 and CD163 are myeloid differentiation markers found primarily on monocytes and macrophages. These markers have been reported as reliable biomarkers of monocyte-macrophage activation, which can be measured as soluble CD14 (sCD14) and CD163 (sCD163) released in plasma and serum.[4]

Monocyte and macrophage activation and inflammatory immune response with the production of a cytokine storm have been described in severe COVID-19 disease.[4] M2- Like anti-inflammatory Macrophage activity in the lungs of COVID-19 patients has been reported in severe lung affection and pulmonary fibrosis.[5] Level of sCD163, the marker for M2-like macrophages detected in the serum of COVID-19 patients, maybe a possible indicator of high M2-like macrophages activity associated with lung damage and pulmonary fibrosis in COVID-19 infection that requires intensive care unit (ICU) admission.[5,6]

sCD14 is a biomarker of monocyte/macrophage activation in COVID-19 infection. In addition, its role in the activation of endothelial cells increases adhesion molecule expression and procoagulant activity, which causes thrombosis in COVID-19 pneumonia.[7] Evaluation of sCD14 in COVID-19 infection reflects an overriding act of monocyte and macrophage immune response in COVID-19 infection.[7]

The pathogenesis of COVID-19 is associated with immune dysregulation and changes in cellular compartments, particularly macrophage M1 and M2 subtypes, which affect the level of released sCD163 and sCD14. These significant immune system changes are also manifested by hematological blood count changes in the form of lymphopenia and increased neutrophil/lymphocyte (N/L) ratio, especially in patients with severe COVID-19 illness.[8,9] The hematopoietic system, blood count, and various hematological parameters are all affected by COVID-19 infection, and these effects may have diagnostic and prognostic significance.[10] Interestingly, emerging evidence links COVID-19 progression and the appearance of variable morphological changes in circulating blood cells and abnormal findings on blood smears.[11,12]

The study aimed to evaluate sCD14 and sCD163 - the monocyte activation markers - as predictors of disease severity and ICU admission in COVID-19 and to investigate their relation to hematological parameters, peripheral blood morphological changes, and inflammatory biomarkers.

Material and Methods.

Research design. This case-control study was carried out for two months and was conducted on 100 subjects. The study included 70 PCR-positive COVID-19 patients admitted to Kasr Al-Ainy Hospital, Cairo University. The sample size was calculated using sample power 3. The power was set at 80% and the alpha level at 0.05. The study complied with the Research Ethics Committee, Faculty of Medicine, Cairo University (N13-2023) and adhered to the guidelines of the Declaration of Helsinki. Written consent was obtained from all participants.

Subjects and material used. The study included 100 subjects. The studied subjects were divided into two groups: Group A included 70 PCR-positive COVID-19 patients with a mean age of 59.93 years, 29 female patients (41.4%) and 41 male patients (58.6%) with a female ratio of 1.4:1. Group B included 30 healthy volunteers with a mean age of 49.7. COVID-19 Patients (group A) were subdivided into two groups: A group of 23 severely diseased patients who required ICU admission and another group of 47 non-ICU admitted patients. Patients were admitted to ICU according to the published World Health Organization Clinical Management of COVID-19 management.[13]

Sample preparation. Seven milliliters of venous blood were collected from each participant and divided as follows: 3 mL of blood in a plain dry sterile vacutainer, samples were allowed to clot at room temperature, and then centrifuged at 3000 g for 10 min. The serum was separated into three aliquots; the first was used to analyze liver and kidney function tests, and the second was used to assay C-reactive protein (CRP), ferritin, procalcitonin, and interleukin-6. The third aliquots were immediately frozen at -20 ^{0}C for assay of sCD163 and sCD14. Two milliliters of blood in sterile K2-EDTA vacutainers were used for complete blood picture and peripheral blood film preparation. Two milliliters of blood were collected on sodium citrate vacutainers, and plasma was separated for Prothrombin time (PT), Partial thromboplastin time (PTT), and D-dimer assays.

Laboratory analysis. The studied subjects confirmed to have COVID-19 by PCR (Cobas 6800 PCR system) were subjected to laboratory investigations: (a) routine tests, including complete blood picture, carried out using a Beckman Coulter LH 750 hematology analyzer, and liver function tests (ALT and AST) and kidney function tests. (Urea and creatinine) carried out using a Beckman Coulter AU680 automated chemistry analyzer (Beckman Coulter, Inc., Brea, CA, USA); (b) immunological tests, including CRP and D-dimer carried out on Cobas c501 while ferritin, interleukin-6 and procalcitonin carried out on Cobas e601 (Roche Diagnostics GmbH, Indianapolis, IN, USA).

Table 1. A summary of demographics, laboratory parameters and peripheral blood smear findings of ICU and non-ICU admitted patients.

	Control Group No.=30	Covid-19 Positive group. No.=70	P-value	Non-ICU admitted No. = 47/70	ICU admitted No. = 23/70	P-value
RBC[c] ($x10^6$/cmm)	4.55 ± 0.56	4.65 ± 0.81	0.542	4.65 ± 0.79	4.67 ± 0.89	0.921
HB[c] (g/dL)	13.27 ± 1.65	12.91 ± 1.71	0.340	13.13 ± 1.49	12.47 ± 2.06	0.134
HCT[c] (%)	38.78 ± 4.35	38.33 ± 5.41	0.688	38.98 ± 4.98	37.00 ± 6.08	0.153
MCV[c] (fl)	85.28 ± 5.60	81.55 ± 8.56	0.031	83.33 ± 4.96	77.91 ± 12.56	0.012
MCH[c] (pg)	29.09 ± 1.93	28.02 ± 2.72	0.054	28.54 ± 2.58	26.94 ± 2.72	0.019
MCHC[c](g/dL)	34.19 ± 1.41	33.92 ± 1.56	0.409	34.02 ± 1.72	33.70 ± 1.16	0.431
RDW[c] (%)	12.66 ± 0.65	14.42 ± 2.07	0.000	14.31 ± 2.32	14.62 ± 1.46	0.564
TLC[b] ($x10^3$/cmm)	5.40 (4.7 – 7.8)	9.25 (6.9 – 11.62)	0.000	8.9 (6 – 11.16)	10.5 (7.2 – 16.3)	0.065
ANC[b]	2.85 (2.3 – 4.8)	7.1 (4.7 – 9.9)	0.000	6.9 (4.3 – 8.8)	8.5 (6.1 – 15.5)	0.029
Abs. lymp[b]	2.3 (1.8 – 2.9)	1.2 (0.6 – 1.9)	0.000	1.2 (0.7 – 2.2)	0.8 (0.4 – 1.4)	0.023
Abs Mono[b]	490 (371 – 720)	0.4 (0.2 – 0.8)	0.000	0 – 2.9	0 – 1.1	0.024
Abs Oes.[b]	79 (55 – 159)	0 (0 – 0.04)	0.000	0 (0 – 0.04)	0 (0 – 0)	0.438
N/L R[b]	1.28 (1 – 1.56)	6.75 (2.77 – 4.4)	0.000	4.3 (2.3 – 12.2)	10.6 (6.5 – 25.2)	0.009
Myelo[b] (%)	0 – 0	0 – 4	0.006	0 – 3	0 – 4	0.074
Meta[b] (%)	0 – 0	0 – 6	0.003	0 – 6	0 – 2	0.444
Staff[b] (%)	0 – 3	0 – 15	0.579	0 – 15	0 – 12	0.885
Plt[b] $x10^3$/cmm)	270.5 (246 – 303)	199.5 (138 – 260)	0.000	214 (151 – 271)	180 (85 – 258)	0.216
MPV[c] (fl)	8.20 ± 3.37	10.16 ± 1.60	0.000	9.86 ± 1.69	10.77 ± 1.22	0.025
Shift to Lt[a]	0 (0.0%)	19 (27.1%)	0.003	10 (21.3%)	9 (39.1%)	0.115
Toxic granulation[a]	0 (0.0%)	15 (21.4%)	0.006	6 (12.8%)	9 (39.1%)	0.012
Neutrophilic vacuolation[a]	0 (0.0%)	5 (7.1%)	0.133	4 (8.5%)	1 (4.3%)	0.525
Plasmacytoid lymphocyte[a]	0 (0.0%)	1 (1.4%)	0.511	0 (0.0%)	1 (4.3%)	0.150
Large granular lymphocyte[a]	0 (0.0%)	1 (1.4%)	0.511	1 (2.1%)	0 (0.0%)	0.481
Monocytic vacuolation[a]	0 (0.0%)	1 (1.4%)	0.511	0 (0.0%)	1 (4.3%)	0.150
Platelet aggregate[a]	0 (0.0%)	6 (8.6%)	0.098	3 (6.4%)	3 (13.0%)	0.350
Giant platelet[a]	0 (0.0%)	8 (11.4%)	0.054	6 (12.8%)	2 (8.7%)	0.615
Platelet satellatism[a]	0 (0.0%)	1 (1.4%)	0.511	1 (2.1%)	0 (0.0%)	0.481
D dimer[b] (mg/L)	0.2 (0.2 – 0.35)	0.5 (0.3 – 0.9)	0.000	0.4 (0.3 – 0.65)	0.9 (0.45 – 2)	0.003
Ferritin[b] (ng/mL)	60 (45 – 117)	525.5 (269.1 – 917)	0.000	400 (198 – 655.7)	926.3 (551 – 1443)	0.001
CRP[b] (mg/L)	2.4 (0.4 – 5)	27.65 (16.3 – 89)	0.000	25 (11 – 65.5)	40.5 (26.5 – 126.7)	0.013
CD 163[b](ng/mL)	245 (151 – 502)	1198 (801 – 1399)	0.000	1064 (779 – 1346)	1335 (1061 – 1480)	0.034
CD14[b] ng/mL)	8.35 (7 – 9)	9.3 (8.6 – 10.7)	0.001	9.3 (8.6 – 10.2)	9.1 (8.5 – 11.1)	0.863

ICU intensive care unit; No number; SD standard deviation; RBC 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; TLC total leucocytic count; ANC absolute neutrophilic count; Abs. lymph absolute lymphocytic count; Abs Oes absolute eosinophils; N/L R neutrophils lymphocyte ratio; Myelo myelocytes, Meta metamyelocytes; Plt platelet and MPV mean platelet volume Shift to Lt shift to left; CRP c-reactive protein. *[a] Data are expressed as n (%), [b] Data are expressed as median [minimum–maximum] (25th–75th percentile) &[c] Data are expressed as mean ± SD.*

sCD163 levels were determined using Elabscience Enzyme-linked immunosorbent assay (ELISA) (Elabscience, Biotechnology Inc. China, catalog number: E-EL-H0036), and levels of sCD14 were determined using SinoGeneClon ELISA (SinoGeneClon, Biotech Co., Ltd, China, catalog number: SG-10117), following the manufacturer's instruction of both kits.

Statistics. Version 23 of the Statistical Package for Social Science (IBM SPSS) was used to gather and analyze the data. The interquartile range and median were used to present quantitative data. Pearson's correlation coefficients were used to study the relationship between sCD14 and sCD163 levels in ICU and non-ICU patients. Values under 0.05 were regarded as significant. Numbers and percentages were used to depict the qualitative data, and the Chi-square test or Fisher exact test was used to compare the groups. When comparing two independent groups with quantitative data and a parametric distribution, the independent t-test was used, whereas the Mann-Whitney test was used for non-parametric distributions. The correlation between two numerical parameters within the same group was evaluated using Spearman correlation coefficients.

Results.

Descriptive data of the studied patients. In this study, the patient group included 41 males and 29 females. Their mean age was 59.93 years. Of 70 COVID-19 patients, 23 (32.9%) had progressive disease requiring ICU admission. Demographics, laboratory parameters, and peripheral blood smear findings of ICU and non-ICU admitted patients are summarized in (**Table 1**).

Serum sCD163 and sCD14 levels in the studied groups. COVID-19 patients had significantly higher levels of sCD163 and sCD14 than the control group (sCD163 median 1198 ng/mL in COVID-19 patients vs. 245 ng/mL in Control group; sCD14 median 9.3 ng/mL in COVID-19 patients vs. 8.35 ng/mL in the control group) (P<0.0001 and P=0.001, respectively). ICU patients had significantly higher levels of sCD163 than non-ICU patients (1135 ng/mL vs. 1064 ng/mL, respectively) (p=0.034). However, there was no statistically significant difference in sCD14 levels between ICU and non-ICU patients (**Table 1**).

The performance of sCD163 as a marker of severe disease and ICU admission. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the usefulness of CD163 as a potential marker to discriminate between ICU and non-ICU admitted COVID-19 patients. A chosen cut-off value of 734 ng/mL demonstrated a sensitivity of 81.16%, specificity of 96.67%, and positive predictive value of 98% with area under the curve of 0.930 (**Figure 1**).

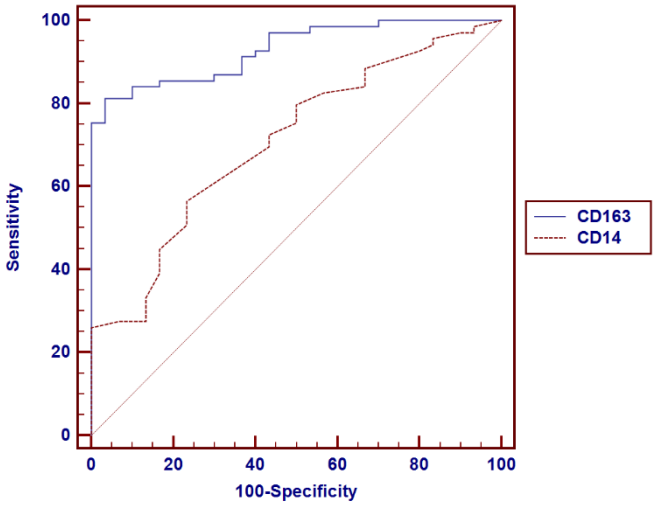

Figure 1. The Receiver operating characteristic (ROC) curve of CD 163 and CD 14 regarding ICU versus non ICU admitted patients.

Comparison of hematological findings among studied groups: changes in total leukocytic count (TLC) and morphology. COVID-19 patients had significantly higher TLC, absolute neutrophilic count (ANC), and N/L ratio than the control group (P<0.001, P<0.001, and P<0.001, respectively) and significantly lower absolute lymphocytic, monocytic, and eosinophilic counts (P<0.001, P<0.001, and P<0.001, respectively). Patients admitted to ICU had a significantly higher N/L ratio (P=0.009) and ANC (P=0.029), as well as a considerably lower absolute lymphocytic (P=0.023) and monocytic count (P=0.024) than non-ICU admitted patients.

The morphological features of the study control, and ICU-admitted and non-ICU-admitted groups were significantly different. COVID-19 patients had considerably more myelocytes, metamyelocytes, shift to the left, and neutrophilic toxic granulation (P=0.003, P=0.006, P=0.006 and P=0.003, respectively) than the control group. The ICU-admitted patients with severe disease had more frequent toxic granulation in the peripheral smear that was significantly more evident compared to non-ICU admitted patients (P=0.012) (**Table 1**, **Figure 2A** and **2B**). Only Five cases out of the 70 studied COVID-19 subjects showed neutrophilic vacuolations (**Figure 2C-2F**)

Changes in red blood cell indices. The patient group had a significantly lower mean corpuscular volume (MCV) (P=0.031) and a significantly higher red cell distribution width (RDW) (P=0.000) than the control group. Patients requiring ICU admission had significantly lower MCV and mean corpuscular hemoglobin (MCH) compared to the non-ICU admitted group (P=0.012 and P=0.019, respectively) (**Table 1**).

Changes in platelets and D-dimer. Abnormal platelet

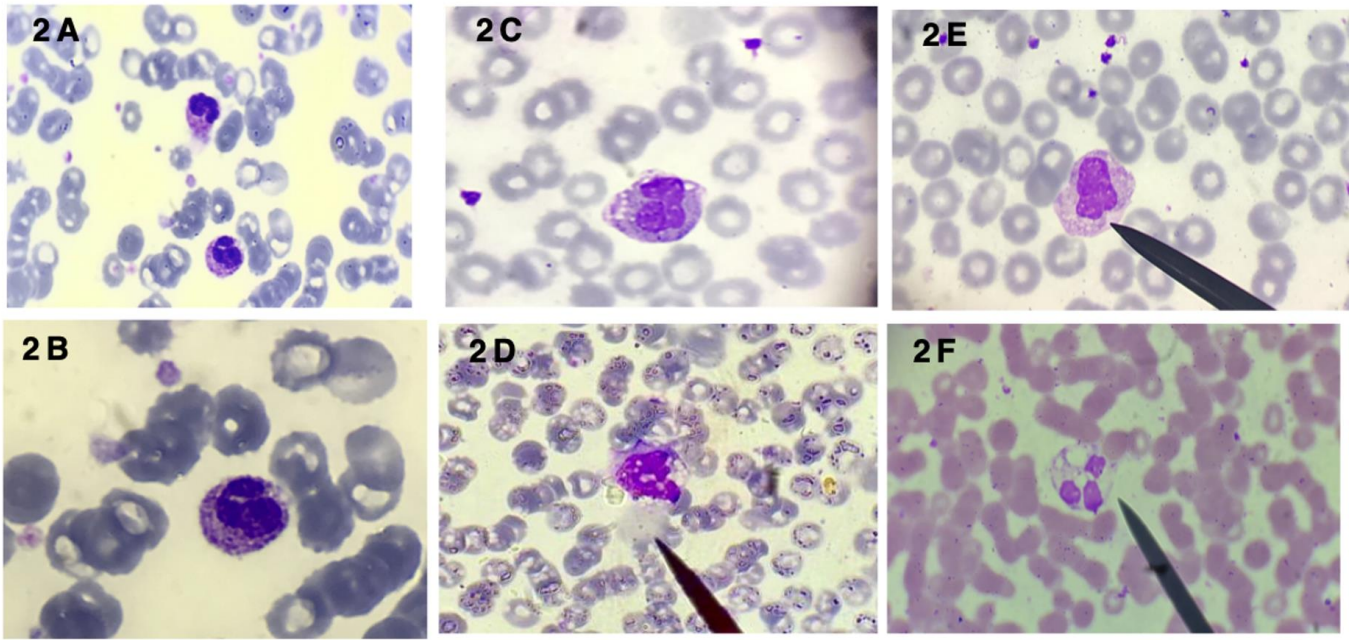

Figure 2. Morphological changes in peripheral blood in COVID-19 infection slides stained using Leishman stain. A and B; Neutrophil granulocyte with marked cytoplasmic hyper-granularity (toxic granulations). C-F; neutrophils vacuolization.

morphological findings were detected, such as platelet aggregation (n=6/70) (**Figure 3E**, **3F**, and **Figure 4B**) and macro-platelets (n=8/70) (**Figure 3A-3D**), but statistical analysis revealed no significant difference between studied groups. Only one critically ill ICU patient had abnormal neutrophil-platelet aggregates (**Figure 4A**). COVID-19 patients had a lower platelet count and higher mean platelet volume (MPV) than the control group (P=0.000 and P=0.000, respectively). Compared to non-ICU admitted subjects, ICU patients had significantly higher MPV (p=0.025).

Patients showed a significantly higher D-dimer than the control group (P<0.001). D-dimer was also considerably higher in ICU patients compared to the non-ICU group (p=0.003)

Changes in inflammatory markers. Inflammatory markers in the form of serum ferritin and CRP levels were significantly higher in patients compared to controls (P<0.001 and P<0.001). Inflammatory markers, ferritin and CRP were also markedly higher in ICU patients compared to non-ICU admitted subjects (P=0.001 and P=0.013, respectively).

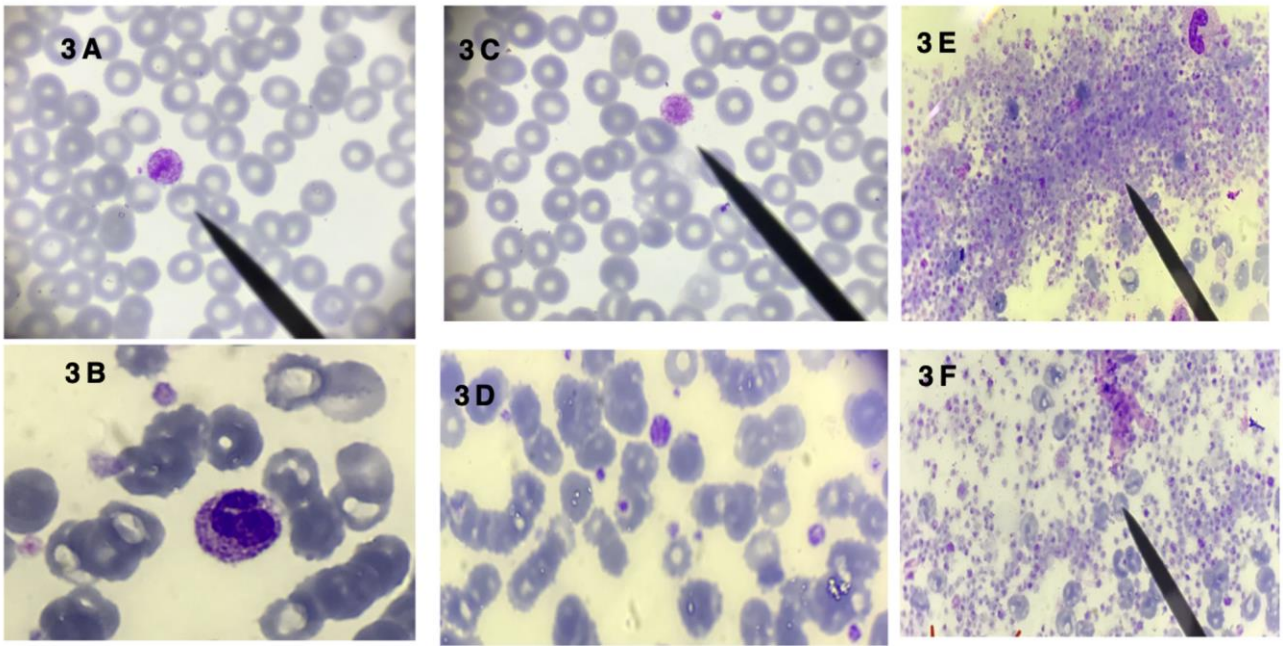

Figure 3. Platelet morphology in COVID-19 infection slides stained using Leishman stain. 3A-3D; macro-platelets. 3E and 3F; platelet aggregates independent of platelet count.

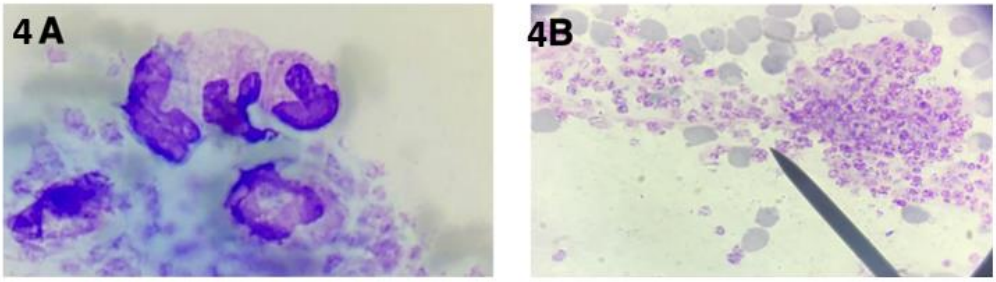

Figure 4. Platelet morphology in COVID-19 infection slides stained using Leishman stain. 4A; Platelet neutrophil aggregates. 4B; Platelet aggregates.

Correlation between sCD163 and sCD14 levels and clinical and laboratory parameters. In COVID-19 patients, levels of sCD163 levels showed positive correlation with TLC (r=0.281, P=0.019), ANC (r=0.325, P=0.006), and N/L ratio (r=0.377, P=0.001). A positive correlation between levels of sCD163 and peripheral smear shift to left in form of myelocytes and metamyelocytes (r=0.290 P=0.016 and r=0.261, P=0.030 respectively) was also detected. There was a negative correlation between sCD163 levels and platelet count (r=-0.256, P=0.033), which could be attributed to platelet activation by monocyte activation in COVID-19 illness.

Interestingly, a positive correlation between levels of sCD14 and D-dimer (r=0.271, P=0.030) was detected. A negative correlation was also found between CD14 levels and INR (r= -0.674, P=0.023) values. High levels of sCD14 were significantly associated with peripheral smear shift to the left and neutrophilic toxic granulations (P=0.036 and P=0.045, respectively).

Discussion. In the present study, we measured sCD163 and sCD14 levels, the monocyte/macrophage activation biomarkers in COVID-19 illness. Monocytes and macrophages have been implicated in the pathogenesis of COVID-19 infection.[4,7,14] The first main group of results in this study were the significantly higher levels of sCD163 and sCD14 levels in sera of COVID-19 patients compared to the control subjects (P<0.0001 and P=0.001, respectively). These findings are consistent with a recent study by Gómez-Rial et al., 2020, who found that COVID-19 pneumonia patients had higher levels of sCD163 and sCD14 than the control group.[4]

In the current study, ICU-admitted patients with severe disease had significantly higher sCD163 levels than non-ICU admitted patients (P=0.034). Zingaropoli et al., 2021 published similar findings, reporting higher sCD163 in patients with COVID-19 progression to acute respiratory distress syndrome (ARDS) (p=0.002).[7] Our results, on the other hand, contradict those of Gómez-Rial et al., 2020 which reported no significant difference in sCD163 levels between ICU and non-ICU admitted patients.[4]

Along with the results of Zingaropoli et al. study in 2021,[7] our findings highlight the clinical utility of sCD163 in determining the severity of COVID-19 pneumonia and support previously reported data of higher sCD163 levels in COVID-19 patients with poor outcome.[7,12,14,15] Furthermore, we discovered a cut-off value of 734 ng/mL for sCD163 serum level, which was related to disease severity and ICU admission (sensitivity 81.16% and specificity 96.67%). Our data highlight the usefulness of sCD163 as a potential marker of predicting severity and may shed light on the early use of monocyte immune-modulating therapy.

CD163 is a scavenger receptor that serves as a marker for M2-like macrophages. The anti-inflammatory and immunosuppressive properties of M2 macrophages aid in tissue repair and wound healing.[4,5] TGF-β and other anti-inflammatory cytokines are secreted by M2-macrophages.[15-18] Kaku et al. 2014 study described a positive correlation between the expression of the M2-macrophage CD163 marker on alveolar cells and disease severity in chronic obstructive pulmonary disease.[6] sCD163 is shed into the serum via a shedding mechanism by the surface membranes of these activated macrophages,[19,20] which explains the significantly higher sCD163 levels in our ICU patients.

Nouno et al., 2019 found M2-alveolar macrophages co-localized with high CD163 expression in interstitial pulmonary fibrosis patients' lungs in serial sections.[21] The findings by Nouno et al., 2019 study explain the significantly higher level of sCD163 in our ICU patients. Our results and previous research highlight the significance of sCD163 levels as a possible indicator of M2-like macrophage activity in the lungs of COVID-19 patients and support the therapeutic targets of macrophage (M2) activation suppression.[11,18-21]

In contrast, we found no statistically significant difference in sCD14 levels between ICU and non-ICU patients. Our findings are supported by a previously reported transient increase in CD14-positive monocytes in mild COVID-19 and its absence in severe COVID-19 infection, which was explained by severe myeloid cell dysregulation.[22,23]

Blood counts are an important tool for estimating disease severity and mortality risk.[24] The second group of results in this study was the significant differences in blood count and peripheral morphology between our study groups, implying that blood picture and peripheral morphology play an important role in determining

disease severity in COVID-19 infection.

Similar to previous research, we discovered that COVID-19 patients had significantly higher TLC, ANC, and N/L ratio (P<0.001, P<0.001, and P<0.001, respectively) and significantly lower absolute lymphocytic, monocytic, and eosinophilic count (P<0.001, P<0.001, and P<0.001, respectively) compared to the control group.[25,26] Patients admitted to ICU had a significantly higher N/L ratio and ANC (P=0.009 and P=0.029) but a considerably lower absolute lymphocytic and monocytic count (p=0.023 and P=0.024). These findings are consistent with the results of previous studies.[26-28]

Regarding the morphological examination of peripheral smears, we identified that COVID-19 patients had significantly more frequent myelocytes, metamyelocytes, shift to the left, and neutrophilic toxic granulation than the control group (P=0.003, P=0.006, P=0.006 and P=0.003, respectively). Similar results were obtained by previously published studies.[29,30] When compared to non-ICU patients, ICU-admitted patients had a significantly higher frequency of toxic granulations in their peripheral smear (P=0.012) (**Figure 2A** and **2B**), which may be explained by a secondary bacterial infection as an underlying cause of disease severity in our ICU admitted patients.

Comparing our morphological findings to previous research, a study published in 2022 by Jain et al., which included 80 COVID-19-positive patients (41 ICU and 39 non-ICU) and 32 COVID-19-negative ICU patients, found similar results. According to Jain et al. study, the overall mean TLC count and ANC were higher in ICU patients compared to non-ICU patients (WBC, 12.43 ± 1.5 vs. 10.8 ± 1.5 $\times 10^3/\mu l$, $p = 0.25$ and mean ANC, 10.60 ± 1.3 vs. 5.32 ± 1.4 $\times 10^3/\mu l$, $p = 0.24$, respectively) with higher frequency of left myeloid shift ($p = 0.021$).[31]

We also reported on other morphological findings, such as neutrophilic vacuolization, identified in five of our 70 COVID-19 patients (**Figure 2C-2F**). COVID-19 illness has been associated with neutrophilic vacuolization in peripheral blood.[28,32] A study by Pozdnyakova et al. 2021 described different morphologic alterations in 100% of patients with COVID-19 (90 patients).[28] The most frequent morphologic finding was cytoplasmic vacuolization, present in multiple cell types with varying frequency, including neutrophils.[28]

To the best of our knowledge, this is the first study to investigate the relationship between sCD14 and sCD163 levels, peripheral blood morphological findings, and other blood count parameters. In our research, soluble CD163 levels correlated positively with the N/L ratio, which has been described as an independent prognostic biomarker in determining COVID-19 prognosis and treatment efficacy.[33-37] In addition to the N/L ratio, a positive correlation was found between sCD163 levels and ANC. The morphological study of COVID-19 patients' blood smears showed a significant association with high CD 163 levels in the form of shift to left and hyper-granular neutrophils with toxic granulations (p=0.003) (**Figure 2A** and **2B**).

Patients with COVID-19 infection had significantly lower platelet count, which correlated negatively with higher sCD163 levels (r=-0.256, p=0.033), indicating that monocytic activation is strongly linked to platelet activation and consumption. Our findings are consistent with a previous meta-analysis on a cohort of 7,613 COVID-19 patients by Jiang et al., 2020, which found that lower platelet count is associated with severe disease and poor outcomes.[38]

Low platelet count is a multifactorial finding in COVID-19 disease.[39,40] Platelet consumption in COVID-19 disease has been attributed to endothelial damage, platelet aggregates in the lung, bone marrow suppression, and immune clearance.[39,40] According to Thachil et al. study in 2020, the formation of pulmonary thrombi is necessary for preventing viremic spread through the bloodstream, has an anti-infective role, and produces platelet consumption.[41]

According to our findings, COVID-19 patients had significantly higher MPV than control subjects. We observed substantially higher MPV values in ICU-admitted patients than in non-ICU patients (p=0.025). Our MPV findings are consistent with the findings of Güçlü et al. study, which described the MPV as a supplementary test in predicting the severity and mortality in COVID-19 patients.[42] The trend toward higher MPV persists even in COVID-19 patients with normal platelet count, according to a study published in 2021 by Wool et al.[43]

These MPV findings may reflect an ongoing platelet activation in COVID-19 infection. The high platelet size has been associated with a high number of surface receptors and increased platelet content of ATP. The larger platelets are active, with a higher potential for protein synthesis and hemostasis.[44] Our results revealed no correlation between MPV values and sCD163 levels.

Regarding platelet morphology, we identified blood smear macro-platelets only in 8 of our COVID-19 patients (**Figure 3-A**, **C**, and **D**). Pezeshki et al. 2021 study, which included 89 hospitalized COVID-19 patients, reported macro-platelets in 42.7% of studied COVID-19 patients.[45] Other studies also reported giant platelets in COVID-19 patients.[46,47] According to prior research, the lung is another source of megakaryocytes where platelets can be derived from this tissue.[48] Given that the COVID-19 virus primarily affects the lungs, there could be an explanation for our findings.

Six out of 70 patients showed platelets aggregates in blood smear (3 ICU admitted and 3 non-ICU admitted patients). Neutrophil-platelet aggregates were also

detected in only one patient (**Figure 4A**). In 2021, Rampotas and Pavord reported platelet aggregates and macro-thrombocytes in blood films of 20 ICU patients with COVID-19 infection, indicating increased platelet activity.[49] The findings of Rampotas and Pavord, combined with ours, could provide additional evidence of platelets' role in COVID-19-related thrombotic complications. We found no significant correlation between platelet aggregates on peripheral blood smears and sCD163 levels.

Regarding D-dimer and other inflammatory markers, highly significant levels of D-dimer, serum ferritin, and CRP were found in the COVID-19-infected group of patients compared to the control group. In line with previous research, D-dimer, serum ferritin, and CRP levels were significantly higher in our ICU patients with disease progression than in non-ICU admitted patients in our study.[49-51] We found no correlation between sCD163 and D-dimer, serum ferritin, or CRP. Similarly, Volfovitch et al., 2022 study discovered that sCD163 levels and ferritin values correlated with the severity of COVID-19 infection, but there was no significant correlation between ferritin rise and sCD163 levels.[52] Similar to our findings, Zingaropoli et al., 2021 discovered no significant relationship between D-dimer and CD163.[7]

In terms of the relationship between sCD14 levels and other peripheral blood findings, our study is the first to show a significant association between high sCD14 levels and left shift and toxic granulations in neutrophils (p=0.036 and 0.045, respectively), but not other white cell changes.

We found a positive correlation between sCD14 levels and D-dimer (r=0.271, P=0.030). Regarding the D-dimer, our findings are consistent with those of Zingaropoli et al., 2021,[7] who discovered a positive correlation between plasma levels of sCD14 and D-dimer, implying a link between monocyte activation and hypercoagulability. Our findings support the previously published hypothesis that sCD14 activates endothelial cells, increasing adhesion molecule expression and procoagulant activity, the main cause of coagulation activation in COVID-19 pneumonia.[7,53] Other studies showed a correlation between TF expression and plasma levels of sCD14, the lipopolysaccharide (LPS) receptor produced by monocytes upon in vivo LPS activation.[54,55]

Conclusions. The data of this study highlight the role of sCD163 as a biomarker of M2-macrophage activation in severe COVID-19 disease. Our findings emphasize the role of monocytes and sCD14 in the activation process of hypercoagulability associated with COVID-19 infection. Furthermore, the differences in sCD163, sCD14 levels, blood count, and peripheral morphology between ICU and non-ICU admitted patients uncover their importance as tools in diagnosing and predicting disease progression. The recognized preliminary data encourage further studies on a larger scale and future clinical trial testing for therapeutic approaches targeting immune-modulation of macrophage/monocyte (M2) response in COVID-19 infection.

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