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Value of hematological parameters for predicting patients with severe coronavirus disease 2019: a real-world cohort from Morocco

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus 2. The clinical manifestations and the evolution of patients with COVID-19 are variable. In addition to respiratory involvement, COVID-19 leads to systemic involvement and can affect the hematopoietic system. This study aimed to evaluate the prognostic value of hematological and hemocytometric parameters in predicting the severity of patients with COVID-19.

Methods: We performed a retrospective study at Mohammed VI university Hospital from 1 March to 11 November 2020. We collected demographic characteristics and hematological findings of incident COVID-19 cases.

Results: A total of 245 patients were included in our study. We found that the rate of lymphopenia was significantly reduced in patients who were severely affected by COVID-19. Additionally, the rate of neutrophilia, the neutrophil side fluorescence light signal, monocyte fluorescent intensity, monocyte size, the neutrophil-to-lymphocyte ratio, the platelet-to-lymphocyte ratio, and the

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lymphocyte-to-monocyte ratio were significantly elevated in patients who were severely affected by COVID-19.

Conclusions: These results are consistent with the literature regarding the predictive value of these markers. A prospective validation in a large population with a longer follow-up is required.

Keywords

Coronavirus disease 2019, hematological parameter, biomarker, neutrophil side fluorescence, lymphopenia, Morocco

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Background

The coronavirus disease 2019 (COVID-19) pandemic is an emerging viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] COVID-19 was first detected in Wuhan, China on 31 December 2019.[2] COVID-19 has caused an estimated 4.8 million deaths and more than 235 million cases worldwide, and 934,828 cases and 14,315 deaths in Morocco.[3] Sars-CoV-2 belongs to the B lineage of β-coronaviruses.[2] The interhuman modes of transmission of SARS-CoV-2 are direct contact, airborne, and fomite droplets.[4] The clinical presentation of this disease is variable, ranging from simple cases with common influenza-like symptoms to severe cases requiring intensive care.[5] The risk of developing a serious or even fatal form of COVID-19 is higher in elderly people and in those with comorbidities.[5] However, any patient, regardless of their age, can develop severe or even fatal forms of COVID-19.[6] The identification of severe forms of COVID-19 based on clinical and biological features is essential. Therefore, identifying predictive biomarkers of disease outcomes is important.

The use of hematological parameters in predicting the prognosis of patients with COVID-19 has been studied.[7–10] These biomarkers are accessible and inexpensive, particularly for settings with limited resources. These biomarkers include white blood cells (WBCs) and their subpopulations, red blood cells (RBCs) and their indices, platelets and their indices, and derived biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-monocyte ratio (NMR). In addition, the latest blood analyzers provide additional hemocytometric parameters, such as neutrophil side scatter (NE-SCC) and neutrophil side fluorescence light (NE-SFL).[11,12] These novel parameters have the potential for management of inflammatory and infectious diseases,[11,12] but they are not well reported in the literature in relation to COVID-19.

To optimize the management of hospitalized patients with COVID-19, this study aimed to determine the prognostic value of hemocytometric parameters in these patients.

Patients and methods

Study design

A retrospective study was conducted from 1 March to 11 November 2020 to determine the demographic patterns, laboratory

findings, and outcomes of incident cases of COVID-19 in patients who were admitted to Mohammed VI University Hospital Center in Oujda, Morocco. The study protocol was approved by the institutional ethical committee for biomedical research in Oujda (CERBO; approval number: 15/2020). Consent for this study was not required because of its retrospective nature.

Participants and eligibility criteria

All patients who were hospitalized for moderate or severe disease and had a positive reverse transcriptase-polymerase chain reaction test (using a nasopharyngeal swab specimen) for Sars-CoV-2 were included in our study. The patients were grouped into severe and moderate patients. We excluded patients who had hemopathic malignancies, those currently undergoing chemotherapy, pediatric patients, and pregnant women. The stratification of patients with COVID-19 was based on the recommendations of the World Health Organization. The criteria for moderate disease were clinical signs of pneumonia (fever, cough, dyspnea, and fast breathing), but no signs of severe pneumonia, including an oxygen saturation $\geq$90% in room air. The criteria for severe disease were clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/minute; severe respiratory distress; or oxygen saturation <90% in room air.[13]

Laboratory analyses

A complete blood count and hemocytometric parameters were assessed at admission using the SYSMEX XN-1000^{TM} Hematology analyzer (Sysmex Corporation, Kobe, Japan). The complete blood count included RBC-related parameters, platelets, lymphocytes, granulocytes, and monocytes. This analyzer also provided a series of qualitative and quantitative parameters, particularly with regard to the state of the activation status of neutrophils and lymphocytes, as previously described.[11,12] The parameters used in this study are shown in Supplementary Table 1.

Statistical analysis

The absolute number and relative frequency are used to describe categorical variables. Values are shown as the mean and standard deviation (SD) for continuous variables if they were normally distributed or as the median and interquartile range if they were not normally distributed. The Kolmogorov–Smirnov test was used to verify the normality of the patients' characteristics. The chi-square or Fisher's exact test was used to compare differences for categorical variables, and Student's t-test or the Mann–Whitney U test was used for continuous variables. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). A two-tailed $\alpha < 0.05$ was considered statistically significant. Data reporting of this study are in accordance with the STROBE guidelines.[14]

Results

The clinical and demographic characteristics and hematological parameters of the enrolled patients are shown in Table 1. A total of 245 patients were included in our study, with a median age of 61 years (interquartile range: 47–70.5) and a sex ratio of 1.05. Among them, 110 (44.9%) patients with severe disease required treatment in the intensive care unit. There was no significant difference in the median age or sex between the groups. Additionally, 45.3% of the study population had comorbidities, with 51.4% in the moderate group and 48.6% in the severe group. Obesity was the only comorbidity that was significantly associated with the disease severity ($p = 0.008$).

The median WBC count and the neutrophil count in the severe group were

Table 1. Demographic, clinical characteristics, and hematological findings of the enrolled patients.

	Total	Moderate disease	Severe disease	p value
All patients, n (%)	245 (100)	135 (55.1)	110 (44.9)	
Clinical and demographic characteristics				
Age in years (median-IQR)	61 (47–70.5) min: 18, max: 91	61 (47–69)	63 (46–73)	0.477
Sex, n (%)				0.304
Women	119 (48.6)	70 (51.9)	49 (44.5)	
Men	126 (51.4%)	65 (48.1)	61 (55.5)	
Comorbidities, n (%)			50 (45.5)	0.367
No	110 (44.9)	60 (54.5)	54 (48.6)	
Yes	111(45.3)	57 (51.4)		
Missing data	24 (9.8)			
Diabetes, n (%)				0.269
No	175 (71.4)	95 (54.3)	80 (45.7)	
Yes	46 (18.8)	22 (47.8)	24 (52.2)	
Cardiovascular disease, n (%)			64 (47.4)	0.441
No	135 (55.1)	71 (52.6)	40 (45.5)	
Yes	88 (35.9)	48 (54.5)		
Pulmonary disease, n (%)				0.428
No	213 (86.9)	112 (52.6)	101 (47.4)	
Yes	8 (3.3)	5 (62.5)	3 (37.5)	
Renal disease, n (%)				0.356
No	217 (88.6)	114 (52.5)	103 (47.5)	
Yes	4 (1.6)	3 (75)	1 (25)	
Obesity, n (%)				**0.008**
No	206 (84.1)	114 (55.3)	92 (44.7)	
Yes	15 (6.1)	3 (20)	12 (80)	
Smoking, n (%)				0.06
No	212 (86.5)	115 (54.2)	97 (45.8)	
Yes	9 (3.7)	2 (22.2)	7 (77.8)	
Others, n (%)				0.311
No	212 (86.5)	111 (52.4)	101 (47.6)	
Yes	9 (3.7)	6 (66.7)	3 (33.3)	
Flagging				
Q-Flag (blasts/abnormal lymph?)	40 (40–60)	40(40–70)	40 (40–50)	0.553
Q-Flag (left shift?)	10 (0–20)	10 (0–10)	10 (0–20)	**0.004**
Q-Flag (atypical lymph?)	10 (0–30)	10 (0–30)	10 (0–30)	0.811
Q-Flag (RBC agglutination?)	70 (60–70)	70 (60–70)	70 (60–70)	0.351
Q-Flag (turbidity/HGB interference?)	90 (90–90)	90 (80–90)	90 (90–90)	0.298
Q-Flag (iron deficiency)	80 (80–80)	80 (80–80)	80 (80–80)	0.792
Q-Flag (HGB defect)	80 (80–80)	80 (80–80)	80 (80–80)	0.923
Q-Flag (fragments)	0 (0–0)	0 (0–0)	0 (0–0)	0.780
Q-Flag (PLT clumps)	10 (00–10)	10 (0–20)	5 (0–10)	0.607

(continued)

Table 1. Continued.

	Total	Moderate disease	Severe disease	p value
Erythrocyte parameters				
RBCs ($10^6/\mu L$)	4.48 (4.10–4.87)	4.54 (4.18–4.92)	4.38 (4.02–4.80)	0.117
HGB (g/dL)	12.97 ± 1.87	13.1 ± 1.9	12.9 ± 1.8	0.466 (t)
HCT (%)	38.8 (36.05–42)	39.1 (36.3–42.3)	38.3 (35.3–41.6)	0.254
MCV (fL)	87 (84.10–90.15)	86.6 (84.3–90.1)	87.4 (84.0–90.2)	0.523
MCHT (pg)	29.50 (28.40–30.55)	29.6 (28.2–30.3)	29.5 (28.4–30.8)	0.466
MCHC (g/dL)	33.70 (32.90–34.60)	33.7 (32.8–34.6)	33.8 (33.1–34.6)	0.481
RDW-SD (fL)	41.40 (38.75–44.80)	41.2 (38.4–44.2)	41.7 (38.9–45)	0.369
RDW-CV (%)	13.10 (12.30–13.80)	13.1 (12.3–13.8)	13.1 (12.2–13.9)	0.658
MicroR (%)	2.10 (1.30–3.15)	2.1 (1.3–3.2)	2.1 (1.4–3.1)	0.991
MacroR (%)	3.7 (3.35–4.10)	3.8 (3.4–4.1)	3.7 (3.3–4.1)	0.722
Platelet parameters				
PLTs ($10^3/\mu L$)	248 (192–318.5)	252 (192–326)	247 (194–310)	0.865
PDW (fL)	13.30 (11.80–15.20)	13.40 (12–15.40)	12.90 (11.60–14.90)	0.109
MPV (fL) (n = 239)	11.08 ± 1.02	11.14 ± 1	11.02 ± 1.06	0.397
P-LCR (%)	32.78 ± 9.61	33.4 ± 9.4	32.1 ± 9.9	0.303
PCT (%)	0.28 (0.21–0.34)	0.28 (0.21–0.35)	0.27 (0.22–0.33)	0.677
Leukocyte parameters				
WBCs ($10^3/\mu L$)	7.68 (5.72–10.63)	7.38 (5.57–9.72)	8.79 (5.84–11.57)	**0.038**
Nes ($10^3/\mu L$)	5.51 (3.73–8.84)	5.10 (3.64–7.86)	6.45 (3.96–10.14)	**0.017**
LYMs ($10^3/\mu L$)	1.12 (0.77–1.74)	1.26 (0.81–1.88)	0.97 (0.67–1.56)	**0.005**
Mos ($10^3/\mu L$)	0.47 (0.34–0.69)	0.48 (0.35–0.68)	0.46 (0.33–0.70)	0.782
Eos ($10^3/\mu L$)	0.02 (0–0.07)	0.03 (0.00–0.09)	0.02 (0.00–0.05)	0.089
BASOs ($10^3/\mu L$)	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.02 (0.01–0.04)	0.751
IGs ($10^3/\mu L$)	0.04 (0.02–0.12)	0.04 (0.02–0.08)	0.05 (0.02–0.20)	0.121
HFLC ($10^3/\mu L$)	0.03 (0.01–0.06)	0.04 (0.01–0.06)	0.03 (0.02–0.06)	0.569
Hemocytometric parameters				
NE-SSC (Ch)	152.18 ± 5.36	152.5 ± 5.6	151.8 ± 5	0.302
NE-SFL (Ch)	49.80 (47.65–52.15)	49.5 (47.4–51.2)	50.6 (47.9–53.5)	**0.019**
NE-FSC (Ch)	87.61 ± 4.63	87.6 ± 4.6	87.6 ± 4.7	0.953
LYM-X (Ch)	82.41 ± 1.79	82.5 ± 1.6	82.3 ± 2	0.380
LYM-Y (Ch)	70.30 (68–74)	70.1 (68–73.6)	71.1 (68–75.7)	0.242
LYM-Z (Ch)	60.04 ± 1.53	60.1 ± 1.5	60 ± 1.5	0.882
MO-X (Ch)	124.20 (122.55–125.85)	124.5 (122.7–126.1)	123.8 (122.5–125.1)	0.128
MO-Y (Ch)	115.38 ± 9.87	114.2 ± 9.3	116.8 ± 10.4	**0.040**
MO-Z (Ch)	64.17 ± 3.23	63.7 ± 3.3	64.7 ± 3	**0.019**
NE-WX (Ch)	315 (306–330.50)	315 (306–329)	317 (306–332)	0.740
NE-WY (Ch)	606 (585–645)	600 (582–634)	612 (591–663)	**0.029**
NE-WZ (Ch)	647 (567–809.50)	680 (566–807)	615 (570–810)	0.955
LYM-WX (Ch)	502 (463–546.50)	500 (461–546)	502 (464–547)	0.424
LYM-WY (Ch)	876 (791.50–967.50)	854 (784–941)	897 (817–988)	**0.025**
LYM-WZ (Ch)	558 (441.50–736)	602 (441–739)	506 (442–730)	0.434
MO-WY (Ch)	682.94 ± 113.38	681 ± 120	686 ± 105	0.712
MO-WZ (Ch)	618 (525–815)	629 (534–820)	589 (496–811)	0.126
NLR	5.06 (2.50–11.39)	4.248 (2.102–7.923)	6.24 (2.78–14.30)	**0.003**
NMR	11.58 (7.40–19.06)	11.27 (6.96–15.48)	12.23 (7.867–21.32)	0.134

(continued)

Table 1. Continued.

	Total	Moderate disease	Severe disease	p value
LMR	2.29 (1.54–3.79)	2.50 (1.74–3.86)	2.19 (1.27–3.22)	**0.024**
ELR	0.019 (0–0.05)	0.020 (0–0.053)	0.018 (0–0.047)	0.255
NBR (n = 233)	294.67 (188.62–483.50)	284.56 (168–443)	331 (193.5–537)	0.113
PLR	196.49 (128.54–388.47)	176.09 (123.03–330.33)	237.38 (146.89–420.69)	**0.016**

Quantitative variables are expressed as the median (interquartile range) or mean ± standard deviation. Qualitative variables are expressed as the absolute frequency and percentage.

In the XN-1000, the probability of abnormal findings is indicated by the Q value, which is based on a scale from 0 to 300 with increments of 10 arbitrary units. In our laboratory, the cut-off for flagging was set at 100. These bold values mean that the result is significant (< 0.05).

IQR, interquartile range; min, minimum; max, maximum; RBCs, red blood cells; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCHT, mean corpuscular hemoglobin content; MCHC, mean corpuscular hemoglobin concentration; RDW-SD, red cell distribution width-standard deviation; RDW-CV, red cell distribution width-coefficient of variation; MicroR, microcytic red cells; MacroR, macrocytic red cells; PLT, platelets; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, platelet larger cell ratio; PCT, plateletcrit; WBCs, white blood cells; Nes, neutrophils; LYMs, lymphocytes; Mos, monocytes; Eos, eosinophiles; BASOs, basophils; IG, immature granulocytes; HFLC, high fluorescence lymphocyte count; NE-SSC, neutrophil side scatter; NE-SFL, neutrophil side fluorescence; NE-FSC, neutrophil forward scatter; LYM-X, lymphocytes on the x-axis; LYM-Y, lymphocytes on the y-axis ; LYM-Z, lymphocytes on the z-axis; MO-X, monocytes on the x-axis; MO-Y, monocytes on the y-axis; MO-Z, monocytes on the z-axis; NE-WX, neutrophil width on the x-axis; NE-WY, neutrophil width on the y-axis; NE-WZ, neutrophil width on z-axis; LYM-WX, lymphocyte width on the x-axis; LYM-WY, lymphocyte width on the y-axis; LYM-WZ, lymphocyte width on the z-axis; MO-WY, monocyte width on the y-axis; MO-WZ, monocyte width on the z-axis; NLR, neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; LMR, lymphocyte-to-monocyte ratio; ELR, eosinophil-to-lymphocyte ratio; NBR, neutrophil-to-basophil ratio; PLR, platelet-to-lymphocyte ratio.

significantly higher than those in the moderate group ($p = 0.038$ and $p = 0.017$, respectively). Lymphopenia was observed in 105 (43%) patients, and the rate of lymphopenia was significantly lower in the severe group than in the moderate group ($p = 0.007$). The monocyte count was elevated in 16% of patients, and this elevation was in 54% ($n = 21$) of patients in the severe group and in 46% ($n = 18$) of patients in the moderate group. There was no significant difference in the RBC or platelet count between the two groups. The Q-Flag (left shift) was used to distinguish immature granulocytes, and there was a significantly greater shift in the severe group than in the moderate group ($p = 0.004$). Furthermore, neutrophils showed a significantly higher NE-SFL signal ($p = 0.019$) and neutrophil distribution width signal on the y-axis ($p = 0.029$) in the severe group than in the moderate group. In addition to lymphopenia, only the fluorescence intensity dispersion of the lymphocyte distribution width of the y-axis was significantly higher in the severe group than in the moderate group ($p = 0.025$). Regarding monocytes, metabolic activity and permeability of the membrane cell (monocyte side fluorescence), as well as the size (monocyte forward scatter), were significantly greater in the severe group than in the moderate group ($p = 0.017$ and $p = 0.04$, respectively). The analysis of hematological parameter ratios showed that the NLR, PLR, and LMR were significantly different in the severe group compared with the moderate group ($p = 0.003$; $p = 0{,}016$; $p = 0.024$, respectively).

Discussion

In this study, we found that that obesity was associated with the severity of

COVID-19. The biological parameters associated with the severity of COVID-19 were neutrophilia, lymphopenia, and the NLR, LMR, and PLR.

SARS-CoV-2 uses angiotensin I-converting enzyme 2 and transmembrane protease serine 2 serine protease to enter the host cells.[15–18] SARS-CoV-2 is responsible for a cytokine storm,[19] which is probably the key factor in the clinical exacerbation and development of acute respiratory distress syndrome, as well as systemic damage.[6,20] Circulating cytokine concentrations are markedly elevated in patients with severe COVID-19, such as interleukin (IL)-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, IFN-inducible protein 10, monocyte chemoattractant protein-1, macrophage protein 1-alpha, and tumor necrosis factor (TNF)-α.[21]

Our study found that the clinical severity of COVID-19 was not associated with sex or age. Many similar studies have shown that the severity of COVID-19 is related to the elderly population and male sex, which is contradictory to our results.[22–25] This discrepancy between studies may be explained by differences in the study population and the study design.

Obesity is a risk factor associated with COVID-19 severity.[26] Leptin is proportional to body fat mass. Therefore, plasma leptin concentrations are increased in individuals with obesity.[26] Leptin coordinates the innate and adaptive responses of T helper cells, induces the proliferation and functions of antigen-presenting cells and monocytes, and stimulates their secretion of pro-inflammatory cytokines (TNF-α, IL-2, or IL-6).[26] Therefore, these features can explain the severity of disease observed in patients with obesity. Sars-CoV-2 infection alters various blood parameters.[7] In our study, lymphopenia and neutrophilia were significantly associated with the severity of COVID-19, which is in accordance with other studies.[27–29] Lymphopenia observed in patients with severe COVID-19 is due to a downregulation in genes involved in T cell activation and function.[30,31] Additionally, massive T-cell death (CD4+ and CD8+ T-cells), which is due to an increased cell surface expression of programmed cell death protein 1 and T-cell immunoglobulin-mucin domain 3, and NKG2A, has been observed.[30,32] Another study suggested that Sars-CoV-2 virus directly infected T-cells.[33] Neutrophils are mainly involved in an early antiviral defense.[34] The proliferation and migration of neutrophils to infected sites is mediated by IL-6, IL-8, TNF-α, interferon-γ, and granulocyte colony-stimulating factor.[34] Additionally, neutrophils stimulate B cells to initiate humoral immunity.[35] However, during COVID-19 infection, studies have shown that neutrophils become cytotoxic, which may exacerbate the immunopathology of COVID-19.[36–38] We previously found that neutrophils showed a proportional increase in the amount of cellular DNA and RNA (NE-SFL), which could be in favor of cellular activation or even direct infection with Sars-CoV-2.[8] Additionally, a significant increase in membrane permeability and the size of the monocytes was observed. This finding may reflect the activation state of these monocytes.[39] However, this difference between moderate and severe COVID-19 groups suggests that these changes could be attributed to Sars-CoV-2.[40] The parameters associated with morphological changes in the peripheral blood count in infection with Sars-CoV-2 need to be studied in depth.

The clinical value of the ratios of blood parameters, such as the NLR and the LMR, in predicting severity and/or mortality is well established, especially in malignancies.[41–43] In our study, the NLR, PLR, and LMR were significantly elevated in severely ill patients with COVID-19. This finding is in line with several studies that identified these markers as independent predictors of poor outcomes in COVID-19.[44–46] This finding can be explained

by lymphopenia leading to a high NLR and PLR.

To the best of our knowledge, our study is the first to investigate the hematological and hemocytometric parameters and their association with COVID-19 outcomes in Morocco. However, our study has some limitations. The main limitations are the retrospective design, a lack of an optimal follow-up, and the limited availability of other patient's data. However, we believe that our results will provide a reference for future studies on inexpensive biomarkers for predicting the prognosis in COVID-19. A perspective external validation study is required in the future to generalize these findings.

Conclusion

This study shows that lymphopenia, neutrophilia, and the NLR, PLR, and LMR are significantly elevated in severely ill patients with COVID-19. Further prospective studies involving a larger population are required to validate these results.

Availability of data and materials

Data are available at a reasonable request

Author contributions

RS and BM developed the concept of the study. AA, AB, MS, BM, IE, ON, and JE participated in collecting the data. AA analyzed the data and wrote the manuscript. RS, MB, and AM reviewed the manuscript writing and provided critical feedback on the manuscript content. SA supervised the project. The final draft was reviewed and approved by all of the authors.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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