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ORIGINAL RESEARCH

MPR and NLR as Prognostic Markers in ICU-Admitted Patients with COVID-19 in Jazan, Saudi Arabia

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Objective: The aims of the current study were to evaluate the importance of MPR and NLR as prognostic markers in ICU-admitted COVID-19 patients and to investigate the impact of COVID-19 on hematological and coagulation parameters in patients from Jazan region of Saudi Arabia.

Methods: This retrospective study was conducted between October 2020 and January 2021 at King Fahad Central Hospital, Jazan region. Medical files, which included the results of complete blood count (CBC), calculated mean platelet volume to platelet count ratio (MPR) and neutrophils-to-lymphocytes ratio (NLR) parameters, coagulation profile and D-dimer test, of 96 (64 male and 32 female) COVID-19-infected patients admitted to the intensive care unit were reviewed. Associations between the test results and COVID-19 infection outcomes (discharged [DC] or passed away [PA]) were measured.

Results: The results of the current study demonstrate overall significant differences in CBC parameters between PA group as compared to DC group ($P < 0.05$). The PA group had a significantly elevated MPR (10.15±12.16 vs 4.04±1.5; $P < 0.01$) and NLR (18.29±19.82 vs 7.35±9.68; $P < 0.01$) as compared to the DC group, suggesting an association between these parameters and mortality. Odds ratios analysis also showed that adjustment for demographic variables and comorbidities did not weaken the observed association.

Conclusion: Elevated MPR and NLR are associated with poor prognosis in COVID-19 patients and could be useful as therapy management indicators.

Keywords: COVID-19, NLR, MPR, ICU, CBC, mortality

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), at the end of 2019, led to devastating effects with increased morbidity and mortality. According to the WHO, as of 26th of July 2021, more than 194 million cases have been reported worldwide, with more than 4 million confirmed deaths.[1] This new Coronaviridae family virus is highly infectious and contagious. It has spread to all countries worldwide and has placed a significant burden on economies and healthcare systems globally. The disease can be asymptomatic or present as mild (eg, fatigue, muscle and backache pain, fever, cough) to severe respiratory illness (eg, pneumonia)[2,3] or as non-respiratory disorders, such as coagulopathy or septic shock.[4] It can also cause systematic syndrome, with various symptoms affecting several organs, including the lungs, liver, kidneys and heart. The severe complications associated with the disease can be fatal and require rapid intervention and

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management.[5] Hence, efforts are needed to develop not only diagnostic approaches and highly effective vaccines but also therapeutic management indicators.

Data from various studies suggest that some routine laboratory tests, such as complete blood count (CBC) and the parameters derived from them, including mean platelet volume to platelet count ratio (MPR) and neutrophils-to-lymphocytes ratio (NLR), could help to diagnose and predict the severity and prognosis of COVID-19.[6,7] It has been suggested that NLR and MPR are valuable prognostic factors, not only in COVID-19 infection[8,9] but also in many respiratory infections[10] and other diseases, including solid tumors and sepsis.[11,12]

NLR is a novel index for inflammation, and it has been used as an indicator of systemic inflammatory response.[13,14] It is a well-established fact that platelets are instrumental in mounting inflammation, as some of the contents released by activated platelets are key factors of inflammation.[9] Although the exact pathophysiological mechanism of increased MPR to predict the adverse prognosis of patients with COVID-19 is unclear, it could be explained on the basis of some observations. Several cytokines produced by inflammation induce thrombopoietin synthesis leading to increased platelet production.[15] Increased consumption of platelets in coagulation, and inflammation results in decreased platelet count, inducing thrombopoietin production, which in turn increases platelet count. Young platelets released from the bone marrow are usually large in size with increased MPV.[16] It has been found that MPV correlates negatively with platelet count.[17] Hence, increased MPV versus low platelet count results in increased MPR.

A proper interpretation of the routinely requested laboratory tests could help clinicians understand the behavior of the virus in its early stages and the functional activity of the virus-targeted organs. The primary aim of the current study was to evaluate the importance of MPR and NLR as prognostic markers in ICU-admitted COVID-19 patients from Jazan region and to investigate the impact of this infection on their hematological and coagulation parameters.

Materials and Methods

The current retrospective study was conducted between October 2020 and January 2021 at King Fahad Central Hospital, Jazan, Saudi Arabia. The medical files of 96 (64 males and 32 females) COVID-19 infected patients, diagnosed with RT-polymerase chain reaction (RT-PCR) test, admitted to the intensive care unit (ICU) were reviewed. These files included CBC, coagulation profile (prothrombin time test [PT], activated partial thromboplastin time test [aPTT]) and D-dimer test results. The NLR and MPR were calculated from the CBC parameters.[9,18] The association between these laboratory results and the outcome of COVID-19 infection was assessed. Patients were admitted to the ICU in line with Saudi admission criteria.[19]

To categorize the disease outcome, the patients were split into two groups: those who had recovered and been discharged were labeled DC, while those who had passed away during their stay in the ICU were labeled PA, following earlier studies.[20,21]

Ethical Considerations

The study was approved by the Jazan Health Ethics Committee (Reference number 2053), Ministry of Health, Saudi Arabia. Informed consent was waived off by the Ethics Committee on a special request due to the retrospective nature of the study. Personal identification and bioinformation of study subjects were neither collected nor disclosed. The data were only accessible to the principal investigator. The study was carried out according to the Declaration of Helsinki.

Statistical Analysis

GraphPad prism version 8 (San Diego, USA) was used for the statistical analysis. The difference between the groups was analyzed using an independent unpaired *t*-test for group comparison and Chi-square test for age comparison. Multivariate analyses were performed using the Stata version 13 software (StataCorp LP, College Station, TX, USA). P-values were determined using a likelihood ratio test. $P < 0.05$ was considered statistically significant. All data are presented as mean ± standard deviation (SD).

Results

Demographic Data and Clinical Characteristics

The data of 96 COVID-19 patients, comprising 64 (66.7%) males and 32 (33.3%) females, were analyzed (Supplementary Table 1). The mean age of the DC group was 56.94 ± 16.62 years and that of the PA group was 63.31 ± 13.94 years ($P > 0.05$; Table 1).

Comorbidity

Of the 96 patients, 11 (11.45%) had no history of any chronic disease, while 85 (88.542%) presented with

Table 1 Demographic and CBC Parameters of Discharged and Passed Away Patients in the Study Groups

	COVID-19 Outcomes		P value
	DC (n=31; 32.3%)	PA (n=65; 67.7%)	
Age	56.94±16.62	63.31±13.94	0.054
WBC (10^9/L)	9.83±4.60	15.81±12.6	0.0122
RBC ($\times10^{12}$/L)	4.40±1.10	3.70±1.11	0.0047
Hb (g/dl)	11.33±3.04	9.66±2.88	0.0103
HCT (%)	35.9±7.27	30.56±9.33	0.0059
MCV (fl)	80.83±10.11	85.28±9.99	0.0452
MCH (pg)	26.22±3.47	26.55±3.27	0.6481
MCHC (g/dl)	32.04±2.22	31.19±2.33	0.9034
RDW (%)	15.73±2.35	18.08±3.29	0.0006
Platelet (10^3/µL)	298±112	159.8 ±117	<0.0001
MPV (fl)	10.55±1.22	11.06±1.61	0.1450
% N	71.15±14.6	84.2±10.22	<0.0001
% L	18.41±11.35	9.24±7.13	<0.0001
% M	6.89±4.94	5.43±4.18	0.1343
% E	1.87±3.17	0.83±1.79	0.0450
% B	0.29±0.36	0.33±0.87	0.8450
ANC (10^9/L)	7.42±4.29	14.15±11.92	0.0031
ALC (10^9/L)	1.59±0.78	1.11±0.87	0.0103
AMC (10^9/L)	0.73±0.42	0.78±0.72	0.7114
AEC(10^9/L)	0.134±0.21	0.07±0.13	0.0669
ABC(10^9/L)	0.031±0.040	0.041±0.05	0.3722
MPR	4.04±1.5	10.15±12.16	0.0090
NLR	7.35±9.68	18.29±19.82	0.0046

Abbreviations: WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red blood cell distribution width; MPV, mean platelet volume; N, neutrophils; L, lymphocytes; M, monocytes; E, eosinophils; B, basophils; ANC, absolute neutrophil count; ALC, absolute lymphocyte count, AMC, absolute monocyte count; AEC, absolute eosinophil count, EBC, absolute basophil count; MPR, mean platelet ratio; NLR, neutrophil-to-lymphocyte ratio.

comorbidities. Of those 85 patients, 15 (15.63%) had hypertension (HTN), 6 (6.25%) had diabetes mellitus (DM) and 29 (30.20%) had both HTN and DM. Twenty-seven (28.12%) patients had either DM or HTN with or without other clinical conditions, such as cardiovascular disease (CVD) or liver or kidney disease, while 8 (8.33%) patients had a single disease, such as thalassemia, Behcet's disease, or chronic obstructive pulmonary disease (COPD). The comorbidity data are summarized in Table 2.

CBC Data

The disease outcome showed that the discharged group (DC) had significantly higher red blood cell (RBC) count, hemoglobin (Hb), hematocrit, and platelet count compared to the passed away (PA) group (P<0.05; Table 1). In addition, the white blood cell (WBC) count, particularly

Table 2 Frequency of Other Clinical Conditions in the COVID-19 Infected Patients Studied

Comorbidity	Number	Percentage
No chronic disease	11	11.458
DM+HTN	29	30.208
HTN	15	15.625
DM	6	6.25
±DM, ± HTN, ± Other diseases	27	28.125
Other diseases	8	8.33
Total	96	100

Abbreviations: DM, diabetes mellitus; HTN, hypertension.

the neutrophil count, was significantly higher in the PA group than in the DC group (P<0.05), although marked lymphopenia was observed in the PA group (Table 1). A comparison of the CBC results of the male and female groups is presented in Supplementary Table 1. There was no statistically significant difference between the male and female groups in terms of CBC parameters.

MPR and NLR

The overall analysis showed that MPR and NLR were significantly lower in DC patients than in the PA group (P < 0.01; Table 1). Further analysis of MPR and NLR showed that the females had a higher MPR and NLR compared to the males (P > 0.05; Supplementary Table 1).

Coagulation Test and D-Dimer

The results of the PT, aPTT and D-dimer tests were similar for the DC and PA groups (P > 0.05; Table 3) and for the male and female groups (P > 0.05; Supplementary Table 2).

Association Between Baseline Variables and COVID-19 Mortality

In the unadjusted model, the odds ratios (ORs) for fatality significantly increased with increased MPR and NLR, and adjustment for demographic variables and comorbidities did not weaken the associations between MPR and NLR

Table 3 Coagulation Profile and D-Dimer Results of Discharged and Passed Away Groups

Parameters	DC	PA	P value
	Mean±SD	Mean±SD	
PT seconds	14.10±2.91	15.56±5.21	0.1677
aPTT seconds	36.39±22.22	35.95±12.78	0.9066
D-dimer µg/mL	4.81±7.54	5.66±7.12	0.6421

Table 4 Association Between Baseline Variables and Mortality Among COVID-19 Patients Admitted to the Intensive Care Unit

Rubrics		PA n=65	DC n=31	uOR	aOR	95% CI	p-value
Age mean (SD)		63.31±13.94	56.94±16.62	1.02	0.99	0.95–1.04	0.989
Sex n (%)	Male Female	40 (62) 25 (78)	24 (37) 7 (21)	1 0.46	1 0.54	0.13–2.29	0.412
DM n (%)	Yes No	37 (71) 18 (58)	15 (20) 13 (41)	1 1.88	1 0.62	0.13–3.01	0.560
HTN n (%)	Yes No	51 (68) 14 (66)	24 (32) 7 (33)	1 1.06	1 2.45	0.42–13.99	0.313
CVD n (%)	Yes No	7 (77) 58 (66)	2 (22) 29 (33)	1 1.75	1 0.97	0.12–7.42	0.983
MPR median (IQR) NLR median (IQR)		6.08 (3.40–11.63) 12.78 (6.88–22.07)	3.91 (2.72–4.94) 4.14 (2.84–8.42)	1.36 1.09	1.37 1.07	1.03–1.81 1.01–1.15	0.027 0.037

Abbreviations: n, number; SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; MPR, platelet count ratio; NLR, neutrophil to lymphocyte ratio; IQR, interquartile range.

and death. There was a 37% increase in the risk of in-hospital mortality per unit increase in MPR (aOR = 1.36; 95% CI, 1.03–1.81; P = 0.027) and a 7% increase in the risk of in-hospital mortality per unit increase in NLR (OR = 1.07; 95 CI, 1.01–1.15, P = 0.037), as shown in Table 4.

Discussion

In this study, the mean age of the patients recruited was higher than that in previous studies of COVID-19 in Saudi Arabia.[18,20,21] The overall WBC count in our PA group study was similar to the very recent reported studies from Saudi Arabia[20,21] and in contrast to some other studies.[18,22–26] Studies have shown that severely infected COVID-19 patients had a higher WBC count than those with mild COVID-19.[27,28] A higher neutrophil count and lower lymphocyte count were observed in the PA group compared with the DC group, which is consistent with previous reports.[28] Lymphopenia has been suggested to be associated with COVID-19 severity and mortality.[29,30] Variations in WBC counts, including neutrophilia and lymphopenia, are a hallmark of COVID-19, which could be attributed to inflammatory response and cytokine storm.[31,32]

Several studies have examined NLR, which is a calculated parameter derived from the proportion of neutrophils and lymphocytes, as a predictive marker for the diagnosis and prediction of the severity and mortality of COVID-19.[18,30,33,34] The current study shows that increased NLR is associated with poor outcomes in severely infected COVID-19 patients, as demonstrated by the high NLR values in the PA group compared to the DC group. A recent study carried out in Saudi Arabia demonstrated that COVID-19 patients in the ICU had significantly higher NLR values than non-ICU patients and healthy controls.[18] Other reports have clearly shown that NLR is higher in severely COVID-19 patients than in patients with moderate or non-severe COVID-19.[35–37] Tatum et al (2020) and Sayed et al (2021) proposed NLR cutoff values of 4.94 and 5.5, respectively, for ICU admission.[18,34] Our study participants, all of whom were admitted to ICU, showed markedly higher NLR values (>5.0), which suggests that NLR is an important prognostic marker of the severity of COVID-19.

Platelets not only play a role in hemostasis and thrombosis but also in inflammation, immunity, cancer and angiogenesis.[38] Mean platelet volume (MPV) has been suggested to have an association with the severity of inflammation.[39] The involvement of platelets and their indices, such as MPV and MPR, in COVID-19 infection is not fully understood. Several studies have demonstrated the importance of platelet count, MPV and MPR in predicting severity and mortality in COVID-19 patients.[9,24] However, a recent study has ruled out the importance of platelet indices in the management of COVID-19.[40]

In our study, we found higher MPR values in the PA group than in the DC group, suggesting its association with severity and poor prognosis of COVID-19. Zhong and Peng (2020) observed similar findings of elevated MPR in COVID-19 patients with severe pneumonia compared to mild cases.[9] Our data showed an association

between increased risk of COVID-19 mortality and increased MPR and NLR values, which is similar to previous reports related to the hospitalization, severity, and mortality of COVID-19 patients.[18,25,26,30,33,37]

Identifying the exact role and mechanism of NLR and MPR in COVID-19 is beyond the scope of this study and requires further research. Hence, it is worth mentioning that the inflammatory response in COVID-19 might participate in the alteration of WBCs and platelet counts.[41,42]

The coagulation profile and D-dimer results in this study showed values within the normal range for PT and aPTT, but D-dimer values were 10 times higher than the normal range. Similar results have been obtained for other groups.[43,44]

Comorbidities such as diabetes, CVD, chronic respiratory disease, cancer and hypertension play a key role in increasing the severity and mortality of many diseases, including COVID-19. Other risk factors, such as obesity and older age, have also been associated with poor outcomes of COVID-19 infection.[45,46]

The current study has some limitations; the most significant one is the size of the cohort, especially in the female group. Thus, further studies are needed to shed light on the exact role of MPR and NLR in the poor prognosis of severely infected COVID-19 patients.

In conclusion, although no association was found between comorbidities and COVID-19 mortality, MPR and NLR were identified as independent risk factors in this study.

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Disclosure

The authors declare no conflicts of interest.

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