ORIGINAL PAPER

The Role of Hemogram-derived Ratios in COVID-19 Severity Stratification in a Primary Healthcare Facility

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) can cause a wide clinical spectrum, ranging from asymptomatic to severe disease with a high mortality rate. In view of the current pandemic and the increasing influx of patients into healthcare facilities, there is a need to identify simple and reliable tools for stratifying patients. **Objective:** Study aimed to analyze whether hemogram-derived ratios (HDRs) can be used to identify patients with a risk of developing a severe clinical form and admission to hospital. **Methods:** This cross-sectional and observational study included 500 patients with a confirmed diagnosis of COVID-19. Data on clinical features and laboratory parameters were collected from medical records and 13 HDRs were calculated and analyzed. Descriptive and inferential statistics were included in the analysis. **Results:** Of the 500 patients, 43.8% had a severe form of the disease. Lymphocytopenia, monocytopenia, higher C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were found in severe patients ($p < 0.05$). Significantly higher neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), neutrophil-to-platelet ratio (NPR), neutrophil-to-lymphocyte-to-platelet ratio (NLPR) and CRP-to-lymphocyte ratio (CRP/Ly) values were found in severe patients ($p < 0.001$). In addition, they have statistically significant prognostic potential ($p < 0.001$). The area under the curve (AUC) for CRP/Ly, dNLR, NLPR, NLR, and NPR were 0.693, 0.619, 0.619, 0.616, and 0.603, respectively. The sensitivity and specificity were 65.7% and 65.6% for CRP/Ly, 51.6% and 70.8 for dNLR, 61.6% and 57.3% for NLPR, 40.6% and 80.4% for NLR, and 48.8% and 69.1% for NPR. **Conclusion:** The results of the study suggest that NLR, dNLR, CRP/Ly, NPR, and NLPR can be considered as potentially useful markers for stratifying patients with a severe form of the disease. HDRs derived from routine blood tests results should be included in common laboratory practice since they are readily available, easy to calculate, and inexpensive.

Keywords: COVID-19, pandemic, hemogram-derived ratios, severity, stratification.

1. BACKGROUND

COVID-19 is an acute inflammatory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). The main spread via respiratory droplets has led to a rapid increase in the number of patients in all geographic areas (2) and on March 11, 2020, the World Health Organization (WHO) classified the previously declared outbreak as a pandemic (3). From March 5, 2020, when the first case was confirmed in Bosnia and Herzegovina to December 2022, 400.941 cases and 16.224 deaths were reported, with a case fatality rate of 4% (4). According to systematic reviews, up to 40% of COVID-19 cases are asymptomatic and the majority of confirmed cases are mild or moderate and do not require hospitalization (5).

COVID-19 infection is characterized by a hyperinflammatory response due to endothelial dysfunction that can lead to a microvascular obstructive thrombo-inflammatory syndrome with organ failure (6). In approximately 3% of cases, pneumonia can be complicated by respiratory failure requiring oxygen supplementation and mechanical ventilation (5). In patients with severe form, pneumonia can rapidly progress to acute respiratory distress syndrome (ARDS) characterized by diffuse pul-

monary vascular permeability and hypoxemia. Severe form can be associated with coagulopathy, septic shock, and even death (5, 7).

The unexpected increase in patient numbers already overburdened healthcare systems worldwide. In addition to medical personnel directly involved in patient care, laboratory personnel were also put under particular pressure, performing additional tests for COVID-19 alongside regular laboratory tests (8). The high number of confirmed COVID-19 cases during the study period and in each wave of infection requires the identification (screening) of patients at risk for developing severe disease as early as possible to provide them with appropriate medical treatment and reduce morbidity and admission to hospital. Patients and healthcare workers can benefit from precise and timely clinical decisions (9), so it is important to determine accurate, simple, and cost-effective prognostic tools for stratifying patients. The results of numerous studies have shown that common laboratory parameters, leukocyte count and its differentials-neutrophils, lymphocytes, monocytes, and basophils (10), as well as the simple inflammatory marker CRP and ESR, are used as biomarkers of systemic inflammation and immune response. Variations of these parameters have been previously reported in COVID-19 patients but their association with disease severity is still under investigation (11). During the pandemic, different approaches were used to identify potential predictive tools for disease severity (12-14). However, recent data have shown that HDRs are significantly associated with adverse disease progression and can be used for early identification of high-risk patients (15).

2. OBJECTIVE

This study aimed to analyze whether HDRs can be used to identify patients who may develop a severe clinical form of COVID-19 and who are at risk of admission to hospital.

3. MATERIAL AND METHODS

Study design

This cross-sectional observational study was conducted between February and April 2021 at the Public Institution Medical Center of Sarajevo Canton during the third COVID-19 wave. According to the recommendations of the Government of Sarajevo Canton and the Ministry of Health of Sarajevo Canton, the main inpatient facility at the primary level of health care was reorganized and COVID centers were established.

Ethical approval

The Ethics Committee of the healthcare facility approved the study protocol (number 01-06-7720-4/21) and the principles of the Declaration of Helsinki were followed.

Study population and data collection

For 500 patients enrolled in this study, we carefully reviewed and collected data from electronic medical records on demographic characteristics, molecular, laboratory, and radiological findings during the first 10 days after symptom onset. In addition, peripheral oxygen saturation (SpO_2) and data on hospitalization were collected. In accordance with WHO recommendations, COVID-19 positivity in symptomatic patients was confirmed by molecular testing (RT-PCR) (16). The laboratory analyzes included complete blood count parameters, ESR, and CRP. Based on the laboratory test results, 13 HDRs were calculated. Their definitions are listed in Table 1.

c	Parameter	Formula
NLR	neutrophil to lymphocyte ratio	(neutrophils) / (lymphocytes)
dNLR	derived neutrophil to lymphocyte ratio	(neutrophils /white cells - neutrophils)
NPR	neutrophil to platelet ratio	(neutrophils) / (platelets)
NLPR	neutrophil to lymphocyte and platelet ratio	(neutrophils / (lymphocytes × platelets)
PLR	platelet to lymphocyte ratio	(platelets) / (lymphocytes)
MNR	monocyte to neutrophil ratio	(monocytes) / (neutrophils)
MLR	monocyte to lymphocyte ratio	(monocytes) / (lymphocytes)
LMR	lymphocyte to monocyte ratio	(lymphocytes) / (monocytes)
LCR	lymphocyte to C-reactive protein ratio	(lymphocytes) / (C-reactive protein value)
CRP/Ly	C-reactive protein to lymphocyte ratio	(C-reactive protein value) / (lymphocytes)
SII	Systemic immune inflammation index	(neutrophils × platelets) / (lymphocytes)
AISI	Aggregate Index of Systemic Inflammation	(neutrophils × monocytes × platelets) / (lymphocytes)
SIRI	Systemic inflammation response index	(neutrophils × monocytes) / (lymphocytes)

Table 1. Definitions of hemogram-derived ratios

Radiologic findings based on chest radiographs were used to detect inflammatory states and to differentiate between unilateral and bilateral pneumonia. The severity of COVID-19 was assessed according to current guidelines and served as the basis for forming study groups (moderate and severe). If lower respiratory tract disease is detected on clinical assessment or imaging and SpO_2 >93%, the condition is defined as moderate. Severe COVID-19 condition patients have SpO_2 <93% and a respiratory rate >30 breaths/min (17). In the results published in this study, patients younger than 18 years, pregnant women, and patients with incomplete data on molecular, laboratory, and radiological findings were excluded.

Statistical analysis

The SPSS for Windows software package (version 26.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excell (version 11. Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis of the data obtained. The normality of the data distribution was determined by the Kolmogorov-Smirnov test. Chi-square test was used to analyze the categorical variables of the patients, which were expressed as a number and percentage. For parametric continued variables, the independent samples t-test was used for analysis and they were presented as a mean and standard deviation. Nonparametric variables were analyzed using the Mann–Whitney U test and presented as the median and interquartile range. ROC analysis was used to investigate the possibility of using the HDRs parameters in differentiating severity of COVID-19 disease. The significance level was set at $p < 0.05$.

4. RESULTS

A total of 500 patients with confirmed COVID-19 infection were included in the study (Table 2). Of them, 56.2% (n = 281) had moderate disease and 43.8% (n = 219) severe disease. All patients (100%) with severe disease required hospi-

Variable		Moderate		Severe		p value
		n	%	n	%	
Gender	Male	142	50.5	136	62.1	0.012
	Female	139	49.5	83	37.9	
Age	Mean ± SD	56.9 ± 13.12		62.11 ± 12.98		< 0.001
	Range	18 - 84		19 - 93		
SpO2	Mean ± SD	95.55 ± 1.43		89.43 ± 6.43		< 0.001
	Range	84 - 98		39 - 96		
X-ray confirmed pneumonia	Unilateral	102	36.3	11	5.0	< 0.001
	Bilateral	179	63.7	208	95.0	

Table 2. Demographic and basic clinical characteristics of study participants according to the severity of disease (N = 500)

talization. Male respondents dominated in both groups (50.5% and 62.2%, respectively). The mean age in the moderate group was 56.9 years and in the severe group 62.11 years. Statistically significant differences were found in gender ($\chi^2 = 6.21$, $p = 0.012$) and age distribution (t = -4.417, $p < 0.001$). Bilateral pneumonia was found in 95% of patients with severe form and in 63.7% with moderate form of COVID-19 ($\chi^2 = 67.050$, $p < 0.001$). There was a significant difference (t = 13.830, $p < 0.001$) in mean SpO_2 values between the moderate and severe groups (95.55 and 89.43, respectively).

Significant differences between moderate and severe patients were found in the following hematologic parameters and inflammatory markers: lymphocyte count 1.29 (0.99-1.8), $p = 0.002$ and monocyte count 0.42 (0.28-0.54), $p = 0.047$ were higher in the moderate group, while CRP 71.1 (33.9-110.2), $p < 0.001$ and ESR 42 (26.3-70), $p < 0.001$ were higher in the severe disease patients (Table 3). Statistically significant differences in other hematological parameters were not confirmed ($p > 0.05$). The median values and interquartile ranges of HDRs for patients with moderate and severe disease are shown in The largest differences were found for the CRP/Ly ratio ($p < 0.001$), where a twofold increase was found in severe patients 61.49 (26.26–102.64) compared with moderate 28.56 (11.85–53.95). In addition, in this group of patients, higher scores for NLR 4.48 (3.29–6.5), $p < 0.001$, dNLR 3.0 (2.22–4.26), $p < 0.001$, NPR 0.025 (0.18–0.34), $p = 0.001$, and NLPR 0.022 (0.013–0.035), $p < 0.001$ were found. Furthermore, higher values for MNR 0.08 (0.06–0.1), $p < 0.001$ and LCR 0.04 (0.02–0.08), $p < 0.001$ were found in moderate patients. No significant differences were found for other HDRs ($p > 0.05$), although SII was closest to the threshold for statistical significance. Higher scores were found in patients with severe disease 1030.07 (585.40–1557.55) compared to patients with moderate disease 912.17 (546–1349.46), $p = 0.071$.

Using ROC analysis, we presented the AUC and cut-off values of HDRs in Table 4 to assess the prognostic potential in predicting disease severity and hospitalization of patients with COVID-19. In our study, five HDRs had statistically significant prognostic potential ($p < 0.001$). The AUC for CRP/Ly was 0.693, for dNLR 0.619, for NLPR 0.619, for NLR 0.616 and NPR 0.603. The sensitivity and specificity for the above ratios were 65.7% and 65.6% for CRP/Ly, 51.6% and 70.8 for dNLR, 61.6% and 57.3% for NLPR, 40.6% and 80.4% for NLR, and 48.8% and 69.1% for NPR. However, the ROC curve analysis of the other HDRs (SII, PLR, MLR, SIRI, AISI, LMR, MNR, and LCR) did not reach a significant level (AUC < 0.6, $p > 0.05$).

Variable	Moderate Median (IQR)	Severe Median (IQR)	p value
Total leukocyte count (x109/L)	7 (5.8-8.7)	7.5 (5.6-9.9)	0.113
Lymphocyte count (x109/L)	1.29 (0.99-1.8)	1.14 (0.88-1.52)	0.002
Neutrophil count (x109/L)	5 (4.02-6.31)	5.4 (3.88-7.22)	0.082
Monocyte count (x109/L)	0.42 (0.28-0.54)	0.37 (0.22-0.55)	0.047
Platelet count (x109/L)	236 (166-315)	212 (154-289)	0.063
Red blood cells (x1012/L)	4.7 (4.39-4.94)	4.66 (4.27-4.97)	0.572
Hemoglobin (g/dL)	13.9 (12.9-14.7)	13.8 (12.8-14.6)	0.307
Hematocrit (%)	0.42 (0.39-0.44)	0.41 (0.39-0.44)	0.342
CRP (mg/L)	35.9 (15.2-62.4)	71.1 (33.9-110.2)	< 0.001
ESR (mm)	32 (20-52)	42 (26.3-70)	< 0.001
NLR	3.84 (2.72 - 4.9)	4.48 (3.29 - 6.5)	< 0.001
dNLR	2.45 (1.87 - 3.15)	3.0 (2.22 - 4.26)	< 0.001
NPR	0.02 (0.02 - 0.03)	0.025 (0.18 - 0.34)	0.001
NLPR	0.02 (0.01 - 0.02)	0.022 (0.013 - 0.035)	< 0.001
PLR	173.26 (127.65 - 246.43)	177.27 (125.68 - 279.76)	0.134
MNR	0.08 (0.06 - 0.1)	0.063 (0.043 - 0.098)	< 0.001
MLR	0.29 (0.21 - 0.39)	0.299 (0.217 - 0.421)	0.238
LMR	3.39 (2.52 - 4.64)	3.36 (2.37 - 4.59)	0.38
LCR	0.04 (0.02 - 0.08)	0.016 (0.009 - 0.038)	< 0.001
CRP/Ly	28.56 (11.85 - 53.95)	61.49 (26.26 - 102.64)	< 0.001
SII	912.17 (546 - 1349.46)	1030.07 (585.40 - 1557.55)	0.071
AISI	362.01 (176.26 - 590.48)	324.96 (153.15 - 772.42)	0.975
SIRI	1.56 (0.91 - 2.24)	1.57 (0.91 - 2.89)	0.283

Table 3. Comparison of biochemical parameters and hemogram-derived ratios according to COVID-19 severity. IQR - interquartile range

5. DISCUSSION

The development of an accurate tool that can predict the clinical course of the disease could be very helpful in patient categorization, clinical decision-making, and administration of certain drugs in order to avoid serious adverse effects. Early detection of patients affected by COVID-19 who will have a worse outcome is an important concern.

Inflammatory markers are widely used tools in predicting the severity of an inflammatory condition. Although ESR is one of the first inflammatory markers, its value in routine practice is decreasing due to the development of new inflammatory markers, but also reduced sensitivity and specificity as a result of the action of numerous factors (18). The present study showed significantly higher ESR values in the severe group of patients compared to the moderate group of COVID-19 patients. A retrospective cohort study by Kaya et al (19) showed similar results, with values significantly higher

Variable	AUC	Std. error	95% CI		p value	Cut off point	Sensitivity (%)	Specificity (%)
			Lower limit	Upper limit				
CRP/Ly	0.693	0.023	0.646	0.739	< 0.001	> 40.33	65.7 (59.1-72.0)	65.6 (59.7-71.2)
dNLR	0.630	0.025	0.579	0.679	< 0.001	> 2.99	51.6 (44.8-58.4)	70.8 (65.1-76.1)
NLPR	0.619	0.025	0.569	0.668	< 0.001	> 0.017	61.6 (54.9-68.1)	57.3 (51.3-63.2)
NLR	0.616	0.025	0.567	0.666	< 0.001	> 5.36	40.6 (34.1-47.5)	80.4 (75.3-84.9)
NPR	0.603	0.025	0.542	0.643	< 0.001	> 0.025	48.8 (42.1-55.7)	69.1 (63.3-74.4)

Table 4. Receiver operating characteristics curves analysis of potential factors in differentiation of COVID-19 disease severity

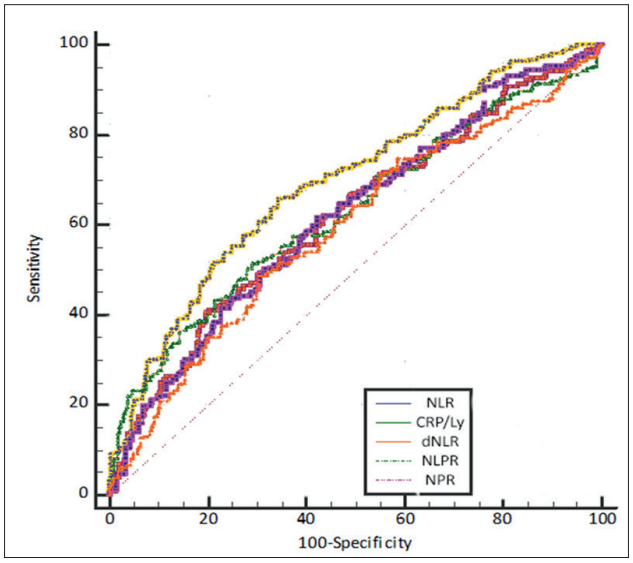

Figure 1. Receiver operating characteristics curves analysis of potential factors in differentiation of COVID-19 disease severity

in the severe group ($p < 0.001$). The authors concluded based on logistic regression analysis that ESR in this case is a valuable biomarker not only in predicting the severity of COVID-19, but also mortality. The development of severe clinical features occurs through the production of pro-inflammatory cytokines that contribute to the development of hematologic changes such as lymphopenia, neutrophilia, and thrombocytopenia, as well as inflammatory markers such as CRP (20). High CRP levels are associated with disease severity during COVID-19 infection. The study conducted by Ahnach et al (21) revealed a significantly higher value of CRP in the severe disease group (3.4 vs 86.5 mg/l, $p < 0.001$). Our results are in line with previous study and also show significantly higher CRP levels in patients with severe clinical features compared with moderate clinical features patients (71.1 vs 35.9 mg/l, $p < 0.001$). The number of lymphocytes in peripheral blood decreases in patients with COVID-19 and the decline depends on the severity (0.8 vs 0.9 x10^9/L; $p = 0.002$) (7). The current study confirmed this finding. A significantly lower lymphocyte count was determined in severe disease patients compared to moderate ones (1.14 vs 1.29 x10^9/L; $p = 0.03$).

Similar to the study of Tonduangu et al (22) who reported higher values of CRP/Ly in severe clinical features group compared to the moderately ill group of patients (163.9 vs 83.0, $p < 0.001$), we noticed higher values of this HDR in a line with severity of the disease (61.49 vs 28.56, $p < 0.001$). The ratio was observed to have better sensitivity during the acute phase, but may be useful as a prognostic biomarker in predicting severity and mortality associated with COVID-19 infection (22). By reviewing the literature, we noticed that the ratio of lymphocytes and CRP was not given special attention. Our study showed that LCR values were significantly lower in the group of patients with more severe disease compared to the group of patients with moderate disease, but ROC analysis did not show prognostic potential in predicting disease severity and hospital admission. Similar results were reported by Erdogan et al (23).

Changes in red blood cell parameters are associated with the progression and severity of COVID-19. It has been observed that count variation occurs before the onset of clinical symptoms, which requires special attention (24, 25). However, in our study, no significant differences were observed in counts of red blood cells, hemoglobin and hematocrit between the group of patients with moderate and severe disease. Similar results were reported by previous studies (24, 26). Although platelets are considered as key participants in the processes of thrombosis and hemostasis, recent studies have reported a complex interaction with neutrophils in inflammation (27, 28). In our study, no difference in platelet count and PLR was noticed between moderate and severe COVID-19 patients. NLPR as a predictive ratio for disease severity in COVID-19 has not been analyzed in a large number of studies. In this study significantly higher values of NPR and NLPR were noticed in patients with severe disease compared to patients with moderate clinical features ($p < 0.001$). Retrospective cohort study conducted in Egypt revealed a significant increase of NLR, PLR, NLPR, SIRI, and CRP/Ly, but also decreased LMR in COVID-19 patients compared to the control group ($p < 0.05$) (29). The cut-off value of NLPR for predicting the risk of disease progression was (95% CI, > 0.010), which is similar to our results (95% CI, > 0.017). In addition, SIRI values did not show a diagnostic potential in our study.

Several studies have confirmed NLR, PLR, and NPR as novel inflammatory markers for the diagnosis and prognosis of COVID-19 infections (23). NLR is a novel inflammatory marker that plays a predictive role in various diseases. Recently, it was shown that this parameter measured at admission has a high capacity to predict disease exacerbation and clinical progression of COVID-19 patients and can be used as a laboratory parameter to differentiate between severe and mild patients (30-32). The results of Wang et al's (30)

meta-analysis, showed that the overall sensitivity and specificity of NLR in predicting severe COVID-19 cases were 0.82 (95% CI, 0.77- 0.87) and 0.77 (95% CI, 0.70-0.83), respectively. The AUC was 0.87 (95% CI, 0.84-0.90), implying that the NLR can accurately predict severe COVID-19 cases. The cut-off value of NLR ranged from 1 to 13.39 due to the physical condition of patients, an increased number of elderly patients with severe COVID-19 and complications associated with a high NLR value. The results of the present study revealing that sensitivity and specificity (40.6% and 80.3%, respectively) and AUC [0.61 (95% CI, 0.567-0.667)] suggest that NLR has potential in predicting the development of severe COVID-19 clinical form. The cut-off value of NLR for severity classification of COVID-19 patients was 5.36 (95% CI, 0.56-0.66).

Xia et al (33) tested the predictive value of NLR and SII in severe COVID-19 patients and found that AUC, optimal cut-off value, sensitivity and specificity were 0.867, 7.25, 70.8%, 92.2%; 0.860, 887.20, 81.2%, 81.8%, respectively. Based on the results, the authors reported that this HDR can be considered as a diagnostic biomarker in severe patients with COVID-19. In this study, the SII did not demonstrate diagnostic potential. Ardestani et al (34) sought to determine the association of NLR, MLR, PLR, and dNLR with severity and outcome of infection, but also to select the best prognostic marker for COVID-19. They found dNLR a reliable marker for the prediction of the severity of disease with its significantly lower values in a group of patients with moderate disease compared to patients with severe disease (2.88 vs 5.33, $p = 0.014$) with AUC = 0.73.

In our study, dNLR values showed similar trends in relation to the severity of COVID-19 (2.45 vs 3.00, $p < 0.001$) with AUC = 0.63 for predicting the severity of the disease.

Monocytes, as integral parts of innate immunity, show certain changes that occur as a result of COVID-19. In this study, the progression of COVID-19 was associated with decreased monocyte counts ($p = 0.047$), while a significant increase of MNR values was reported in moderate COVID-19 patients ($p < 0.001$). Previous studies reported similar findings (35, 36). The reduced number of monocytes in COVID-19 at different severity of the disease can be associated with the development of an ARDS, as indicated by numerous literature data (37). In addition, MNR values in our study did not show a prognostic potential, compared to Kilerick study ($p < 0.001$) (36). Based on previous findings, we sought to identify a set of risk factors to point out patients at risk of hospitalization due to a severe form of COVID-19. Models to predict the severe clinical form and risk of admission to hospital–HDRs should be included in laboratory reports to help identify moderate-to-severe cases of COVID-19 and to notify on the hyperinflammatory state and microvascular occlusion associated with moderate-to-severe cases. The combination of several parameters derived from the hemogram (routine variables-white blood cells, lymphocytes, monocytes, and platelets) could help in the decision to apply a more vigorous therapeutic setting with anti-inflammatory treatments in case of worsening. HDRs are readily available, easy to measure, routine, and affordable in any healthcare setting.

In our study, ROC analysis showed that NLR, dNLR, CRP/Ly, NPR, and NLPR had prognostic value in assessing disease severity. The AUC value in the study was highest for CRP/Ly 0.692, dNLR 0.629, NLPR 0.618, NLR 0.616, and NPR 0.603. The highest sensitivity in predicting the risk of disease severity had CRP/Ly (65.75%, cut-off > 40.33), while the highest specificity was observed for NRL (80.43%, cut-off > 5.36). Similar results were observed in previous studies (29, 38-40). The results of PLR, MLR, LMR, SII, AISI and SIRI showed no evidence of the prognostic potential of COVID-19 severity. Optimal cut-off values for hematologic ratios in COVID-19 were not determined.

A great number of authors considered the main reason for the differences in cut-off values to be related to varieties of the population demographic characteristics, the presence of various comorbidities, and the techniques used to determine cut-off values especially during COVID-19 pandemic era and Long Covid time (38, 41-50).

6. CONCLUSION

Study results indicated that NLR, dNLR, CRP/Ly, NPR, and NLPR can be considered as potentially useful markers for early stratification of patients with a severe form of COVID-19 in primary healthcare facilities in terms of ensuring them with appropriate support. HDRs derived from routine blood tests results should be included in common laboratory practice since they are readily available, easy to calculate, and inexpensive.

Limitations of the study

Presented study had some unavoidable limitations. This was a single-center study that included only patients in the Canton Sarajevo region. Parameters were collected and measured at the moment of patients' visit at COVID-19 center and their statements about onset of symptoms have been collected and incorporated into study data.

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