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ORIGINAL RESEARCH

Neutrophil/Lymphocyte Ratio (NLR) and Lymphocyte/Monocyte Ratio (LMR) – Risk of Death Inflammatory Biomarkers in Patients with COVID-19

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Aim: The aim of our retrospective study was search for new prognostic parameters, which can help quickly and cheaply identify patients with risk for severe course of SARS-CoV-2 infection.

Materials and Methods: The following peripheral blood combination biomarkers were calculated: NLR (neutrophil/lymphocytes ratio), LMR (lymphocyte/monocyte ratio), PLR (platelet/lymphocyte ratio), dNLR (neutrophils/(white blood cells − neutrophils)), NLPR (neutrophil/(lymphocyte × platelet ratio)) in 374 patients who were admitted to the Temporary Hospital no 2 of Clinical Hospital in Bialystok (Poland) with COVID-19. The patients were divided into four groups depending on the severity of the course of COVID-19 using MEWS classification.

Results: The NLR and dNLR were significantly increased with the severity of COVID-19, according to MEWS score. The AUC for the assessed parameters was higher in predicting death in patients with COVID-19: NLR (0.656, p=0.0018, cut-off=6.22), dNLR (0.615, p=0.02, cut-off=3.52) and LMR (0.609, p=0.03, cut-off=2.06). Multivariate COX regression analysis showed that NLR median above 5.56 (OR: 1.050, P=0.002), LMR median below 2.23 (OR: 1.021, P=0.011), and age >75 years old (OR: 1.072, P=0.000) had a significant association with high risk of death during COVID-19.

Conclusion: Our results indicate that NLR, dNLR, and LMR calculated on admission to the hospital can quickly and easy identify patients with risk of a more severe course of COVID-19. Increase NLR and decrease LMR have a significant predictive value in COVID-19 patient's mortality and might be a potential biomarker for predicting death in COVID-19 patients.

Keywords: COVID-19, biomarker, mortality, NLR, dNLR, LMR, PLR

Introduction

In the last three years, infections with the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) coronavirus have been responsible for almost 6.5 million deaths worldwide due to severe and even fatal respiratory disease known as Coronavirus disease-19.[1] More than 600 mln people around the world were infected with SARS-CoV-2 which causes not only health issues but also unprecedented social and economic problems as well.

Inflammatory damage to cells related to viral replication leads to the release of numerous cytokines and chemokines eg: IL-1β, IL-2, IL-6, IL-8, IL-10, IL-17, TNF-α and CCL-2, and CCL-3 from activated macrophages.[2–5] These cytokines activate the immune response, leading to hyperinflammation known as the "cytokine storm" and the severity of the disease

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process may result in acute respiratory distress syndrome (ARDS).[6–8] Increasing the severity of the inflammatory response leads to its imbalance. Among the known and clinically useful indicators of inflammation, such as C-reactive protein (CRP), procalcitonin (PCT), ferritin, interleukin 6 (IL-6) has also gained an important role in the course of COVID-19, and associated with a high risk of COVID-19 severity.[9,10] There are numerous prognostic scales associated with mortality risk in patients with COVID-19, eg Pneumonia Severity Index,[11] NEWS (National Early Warning Score)[12] and CURB.[13] In Poland, the MEWS (Modified Early Warning Score) was the most commonly used scale in clinical practice. It is based on respiratory and heart rate, systolic blood pressure, blood temperature, and neurological symptoms.[14]

Since blood cells (neutrophils, lymphocytes, monocytes, and platelets) play an important role in the systemic immune response (SIR), their quantification can be an indirect indicator of SIR in patients suffering from a variety of inflammatory diseases, including COVID-19. Complete blood count, as a relatively cheap and widely available test, provides information on the quantitative composition of the main categories of blood cells. In addition to basic parameters such as the number of leukocytes, erythrocytes, and platelets, it also allows for the quantitative assessment of individual subpopulations of leukocytes. The indicators calculated from the complete blood count that could be used in routine diagnostics include NLR (neutrophil-to-lymphocyte ratio), dNLR (derived NLR), LMR (lymphocyte-to-monocyte ratio), PLR (platelet-to-lymphocyte ratio), and NLPR (neutrophil-to-lymphocyte platelet ratio).[15–17] The importance of these indicators has recently grown not only in diagnostics, but also in providing promising predictive biomarkers in many diseases, such as cancer,[15,16,18] acute coronary syndrome (cardiovascular diseases), systemic diseases (eg rheumatoid arthritis and systemic lupus erythematosus),[19,20] but as of late also in the course of COVID-19.[16,21] Their values correlate with a severe course of the disease, a less favorable prognosis, and shorter OS (overall survival).[22–24]

As it is widely known, the SARS-CoV-2 virus is characterized by high infectivity, and in some patients, it is accompanied by serious complications and high mortality, especially in elderly age. Therefore, the search for new prognostic parameters which can help quickly and cheaply identify patients at risk of a severe course of SARS-CoV-2 infection is extremely important and anticipated. The improvement of such diagnostics is the main goal facing modern medicine. Taking the above into account, the aim of the study was to evaluate the diagnostic usefulness and prognostic value of systemic inflammatory biomarkers (NLR, dNLR, LPR, LMR, NLPR) in patients with COVID-19 according to the MEWS classification.

Materials and Methods

We conducted our research by retrospectively reviewing the medical records of patients with COVID-19 after receiving the consent of the Bioethics Committee of the Medical University of Bialystok, Poland (Permission number No APK.002.353.2021). The study was conducted in accordance with the World Medical Association Declaration of Helsinki for ethical principles for medical research involving human subjects. After a thorough explanation of the purposed study and possible risk, all patients gave their informed consent for inclusion before they participated in the study.

Demographic and Clinical Characteristics of Patients

The study included 374 patients (183 women, 191 men; mean age 67 years) who were admitted to the Temporary Hospital no 2 of the Clinical Hospital in Bialystok (Poland) between November 2020 and November 2021 (Table 1). All patients who tested positive with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) nasal and pharyngeal swab specimens before admission were recruited for the study. The severity of COVID-19 was evaluated on the basis of the Modified Early Warning Score (MEWS) scale recommended by the Polish Association of Epidemiologists and Infectiologists[14] which includes the following parameters: systolic BP, heart rate, respiratory rate, temperature, and AVPU score (alert, voice, pain, unresponsive). The patients were divided into four groups according to their MEWS score: stage 1st is asymptomatic or oligosymptomatic, stage 2nd is symptomatic with pneumonia without signs of respiratory failure, and MEWS <3 points, stage 3rd is characterized by severe pneumonia with respiratory failure/pre-ARDS, MEWS 3–4 points and 4th is ARDS/multiple organ failure (MEWS> 4 points) (Table 1).[14]

Table 1 Modified Early Warning Score (MEWS).[14]

Score	3	2	1	0	1	2	3
Respiratory rate, breaths/min		≤8		9–14	15–20	21–29	>29
Heart rate, bpm		≤40	41–50	51–100	101–110	111–129	>129
Systolic blood pressure, mm Hg		71–80	81–100	101–199		≥200	
Hourly urine, mL/kg of body weight/h	Nil	<0.5		>0.5			
Body temperature, °C		≤35	35.1–36	36.1–38	38.1–38.5	≤38.6	
Neurological symptoms				Aware	Responsive to voice	Responsive to pain	Unresponsive

Clinical Characteristics and Laboratory Data

Epidemiological characteristics, including recent exposure history, clinical symptoms, comorbidities, treatment data, computed tomographic scan (CT), and laboratory results were collected from the electronic medical records network. All patients had a routine blood examination including CBC, coagulation profiles, and biochemical tests, in addition to CT and X-ray scans that were done on admission to hospital. Then, the patients were treated in accordance with the diagnosis and treatment plan for COVID-19 depending on the clinical condition, and the treatment procedures were followed until improvement of the patient's condition or death.

In our retrospective study, we used the following parameters: sex, age, hospitalization time, death, presence of comorbidities (yes, no), presence of pneumonia (yes, no), hematological disorders (yes, no), diabetes (yes, no), hypertension (yes, no), obesity (yes, no), heart diseases (yes, no), cancers in history (yes, no); applied treatment – remdesivir (yes, no), antibiotics (yes, no), plasma of convalescents (yes, no), intubation (yes, no), mechanical ventilation (yes, no); clinical symptoms: fever (yes, no), cough (yes, no), shortness of breath (yes, no), acute respiratory distress syndrome (yes, no), gastrointestinal symptoms (yes, no), general condition at the admission, the severity of clinical symptoms according to the Modified Early Warning Score (MEWS) scale, blood pressure, tachypnea (yes, no), pulse, and oxygen saturation. Laboratory assessments consisted of complete blood count (CBC) – which included total WBCs, neutrophils, lymphocytes, monocytes, and platelets; blood chemistry analyses – alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, total bilirubin, creatine kinase (CK), chloride levels (Cl^-), C-reactive protein (CRP), fibrinogen, glucose, ferritin, potassium (K^+), gamma-glutamyl transferase (GGT), creatinine, estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), sodium (Na^+), procalcitonin (PCT), urea, blood urea nitrogen (BUN), interleukin 6 (IL-6), troponin I (hsTnI) and coagulation profiles – activated partial thromboplastin time (APTT) and ratio, prothrombin time (PT) and activity, international normalized ratio (INR) and D-dimer.

Systemic Inflammatory Ratios

The following inflammatory ratios/SIR biomarkers were calculated from CBC: NLR (neutrophil/lymphocyte ratio), LMR (lymphocyte/monocyte ratio), PLR (platelet/lymphocyte ratio), dNLR (neutrophils (white blood cells)), and NLPR (neutrophil/(lymphocyte × platelet ratio)).

Statistical Analysis

The statistical analyses were conducted with Statistica 13.3 (StatSoft, Poland) and STATA/SE 17.0. Descriptive statistics were given as the number of units (n), percentage (%), median (M), 25th percentile (Q1), and 75th percentile (Q3). The compliance of the data of continuous variables to normal distribution was evaluated using the Shapiro–Wilk test and Q-Q graphics. A non-parametric Kruskal–Wallis test with a post-hoc multiple-comparison test was used to compare several quantitative independent variables. Pearson's χ^2 test was used for verifying the relationship between qualitative features. In order to assess the predictive power of the variables, ROC curves were created and AUC was calculated. Kaplan–Meier curves that show survival probabilities were used to present data on survival analysis. Differences between

survival curves were assessed using the Log rank test. A multivariable Cox's hazards model was created to assess the strength of the impact of potential predictors of death from COVID-19. And $p < 0.05$ value was considered statistically significant.

Results

General Patient Characteristics

Detailed characteristics of the study group are shown in Table 2.

A total of 374 patients (183 women, 191 men) diagnosed with COVID-19 were included in the study and followed up during hospitalization. About half of the patients (57%) were aged 56–75 years. The most common symptoms of COVID-19 were cough (69%), chest dyspnoea (67,2%), fatigue (64%), fever (64,4%), and muscle aches (38,2%). Less

Table 2 Clinical Characteristics of Patients with COVID-19

Clinical Features	All Patients with COVID-19	COVID-19 Severity According to MEWS				χ^2	p
	n (%)	1	2	3	4		
Number of patients	374	50 (13.4%)	194 (51.9%)	104 (27.8%)	26 (6.9%)		
Age						9.989	0.1251
≤55	64 (17%)	13 (20.31%)	32 (50.00%)	15 (23.44%)	4 (6.25%)		
56–75	211 (57%)	20 (9.62%)	104 (50.00%)	69 (33.17%)	15 (7.21%)		
>76	99 (26%)	11 (11.22%)	44 (44.90%)	30 (30.61%)	13 (13.27%)		
Sex						3.182	0.282
Female	183 (49%)	22 (12.09%)	80 (43.96%)	61 (33.52%)	19 !0.44%)		
Male	191 (51%)	22 (11.70%)	100 (53.19%)	53 (28.19%)	13 (6.91%)		
Hospitalization time						15.934	0.014
≤10	131 (35%)	16 (12.50%)	54 (42.19%)	39 (30.47%)	19 (14.84%)		
10–20	181 (48%)	23 (12.78%)	99 (55.0%)	51 (28.33%)	7 (3.89%)		
>20	62 (17%)	5 (8.06%)	27 (43.55%)	24 (38.71%)	6 (9.68%)		
Comorbidities (n, %)						6.357	0.095
Absent	51 (14%)	8 (15.69%)	31 (60.78%)	9 (17.65%)	3 (5.88%)		
Present	323 (86%)	36 (11.29%)	149 (46.71%)	105 (32.92%)	29 (9.09%)		
Hypertension	194 (52%)	21 (10.94%)	88 (45.83%)	65 (33.85%)	18 (9.38%)		
Diabetes mellitus	74 (20%)	6 (8.11%)	37 (50.0%)	22 (29.73%)	9 (12.16%)		
Obesity	36 (10%)	2 (5.56%)	17 (47.22%)	9 (25.00%)	8 (22.22%)		
Coronary heart failure	97 (26%)	10 (10.31%)	41 (42.27%)	34 (35.05%)	12 (12.37%)		
Others (eg cancers)	64 (17%)	7 (10.93%)	34 (53.13%)	17 (26.56%)	6 (9.37%)		
Symptoms							
Cough						4.143	0.246
Yes	154 (41%)	19 (12.50%)	81 (53.29%)	38 (25.00%)	14 (9.21%)		
No	220 (59%)	25 (11.47%)	99 (45.41%)	76 (34.86%)	18 (8.26%)		
Fever						4.162	0.244
Yes	241 (64%)	27 (11.25%)	125 (52.08%)	71 (29.58%)	17 (7.08%)		
No	133 (36%)	17 (13.08%)	55 (42.31%)	43 (33.08%)	15 (11.54%)		
Dyspnea						4.077	0.253
Yes	251 (67%)	27 (10.93%)	117 (47.37%)	84 (34.01%)	19 (7.69%)		
No	123 (33%)	17 (13.82%)	63 (51.22%)	30 (24.39%)	13 (10.57%)		
Gastrointestinal symptoms						1.058	0.787
Yes	85 (23%)	10 (11.90%)	43 (51.19%)	26 (30.95%)	5 (5.95%)		
No	289 (77%)	34 (11.89%)	137 (47.90%)	88 (30.77%)	27 (9.44%)		

(*Continued*)

Table 2 (Continued).

Clinical Features	All Patients with COVID-19	COVID-19 Severity According to MEWS				χ^2	*p*
	n (%)	1	2	3	4		
Respiratory failure						2.786	0.425
Yes	127 (34%)	30 (12.30%)	124 (50.82%)	75 (30.74%)	15 (6.15%)		
No	247 (66%)	16 (12.82%)	69 (58.97%)	28 (23.93%)	5 (4.27%)		
Treatment							
Remdesivir						2.208	0.530
Yes	69 (18.5%)	5 (11.63%)	27 (62.79%)	10 (23.26%)	1 (2.33%)		
No	305 (81.5%)	40 (12.58%)	166 (52.20%)	93 (29.25%)	19 (5.97%)		
Antibiotics						8.386	0.040
Yes	324 (87%)	34 (10.63%)	152 (47.50%)	105 (32.81%)	29 (9.06%)		
No	50 (13%)	10 (20.00%)	28 (56.00%)	9 (18.00%)	3 (6.00%)		
Convalescent plasma						5.659	0.129
Yes	46 (12%)	4 (8.89%)	16 (35.56%)	19 (42.22%)	6 (13.33%)		
No	328 (88%)	40 (12.31%)	164 (50.46%)	95 (29.23%)	26 (8.00%)		
Death						88.831	<0.0001
Yes	43 (12%)	1 (2.38%)	3 (7.14%)	20 (47.62%)	18 (42.86%)		
No	331 (88%)	43 (13.11%)	177 (53.96%)	94 (28.66%)	14 (4.27%)		

Abbreviation: MEWS, Modified Early Warning Score.

common symptoms include dizziness/headache, lack of taste and smell, gastrointestinal symptoms, and sore throat. The duration of symptoms was 5.8 days and the duration of hospitalization was 14 days (±9 days). The average HR and oxygen saturation were 89.7% and 84%, respectively.

Patients were divided into four groups according to MEWS classification (Table 1). In stage 1 (asymptomatic) the total number of patients was 50, in stage 2 (symptomatic with pneumonia without signs of respiratory failure) – 194, in stage 3 (severe pneumonia with respiratory failure/pre-ARDS) – 104 and in stage 4 (ARDS/multiple organ failure) – 26. Hospitalization time was less than 10 days in 35% of patients, in 48% of patients, it was 10–20 days and in 17% of patients, it lasted longer than 20 days. Interestingly, about 86% of patients had comorbidities. The most common of them were hypertension (52%), coronary heart failure (26%) and diabetes mellitus (20%), and obesity (10%). Among all symptoms, fever and dyspnea were the most common and were observed in 64% and 67% of patients. Antibiotics were administered in 87% of patients, whereas just 18.5% received Remdesivir. Convalescent plasma was used in 12% of patients. Abnormalities in chest CT images were detected in 87% of patients. Pneumonia was observed in 79% of patients, respiratory failure – in 34%, 11% of patients were intubated, and mechanical ventilation was required in 24% of patients. A 43 (12%) of patients with COVID-19 died.

Basic Laboratory Tests

We compared the selected results of laboratory tests conducted on the day of hospital admission and grouped the patients in accordance with the MEWS classification. Most of the analyzed parameters showed an increased tendency with an increase in the degree of clinical deterioration. Only in the case of WBC (p=0.0419), neutrophils (p=0.0147), creatinine level (p=0.0069), LDH activity (p=0.0222), CRP (p=0.0037), and IL-6 (p=0.0000) the differences between the four analyzed groups were statistically significant (Table 3).

SIR Biomarkers

Statistical analysis performed with the Anova Kruskal–Wallis test revealed that values of NLR and dNLR between the four groups of patients divided according to the MEWS classification differ in a statistically significant manner (p=0.0117, p=0.0224, respectively) (Figure 1, Table 4).

Table 3 Comparison of Chosen Laboratory Tests Results Between Four Groups of Patients with COVID-19 Divided According to MEWS Classification. Results are Presented as Mean Value with Q1-Q3

COVID-19 Severity (MEWS)	1	2	3	4	Anova Kruskal–Wallis Test
WBC [x10^3/μL]	6.438 (4.800–8.250)*	7.199 (4.650–7.940)	7.820 (5.040–9.240)	10.819 (5.435–10.375)	p=0.0419
Neutrophils [x10^3/μL]	4.681 (3.020–6.680)*,#	5.129 (3.140–6.170)	6.562 (3.630–7.600)	7.309 (3.490–8.475)	p=0.0147
Lymphocytes [x10^3/μL]	1.249 (0.805–1.350)	1.326 (0.610–1.330)	1.295 (0.615–1.175)	1.109 (0.470–1.505)	p=0.1473
Monocytes [x10^3/μL]	0.523 (0.280–0.670)	0.616 (0.270–0.600)	0.424 (0.245–0.565)	1.718 (0.270–0.685)	p=0.0980
RBC [x10^6/μL]	4.327 (3.915–4.865)	4.306 (3.970–4.660)	4.220 (3.860–4.660)	4.303 (3.905–4.770)	p=0.6029
PLT [x10^3/μL]	237.545 (160.500–266.000)	202.780 (147.000–248.000)	200.333 (129.000–258.000)	205.250 (127.000–303.000)	p=0.7166
MPV [fl]	10.559 (9.850–11.300)#	10.754 (10.000–11.400)	11.030 (10.300–11.600)	10.977 (10.200–11.600)	p=0.0357
Creatinine [mg/dl]	0.988 (0.7850–1.150)*,#	1.006 (0.780–1.130)	1.050 (0.7650–1.180)	1.29 (0.950–1.47)	p=0.0069
LDH [U/l]	420.269 (280.000–493.000)	458.459 (323.000–561.000)	508.705 (350.000–647.000)	535.04 (415.000–667.000)	p=0.0222
INR	1.614 (1.080–1.300)*	1.796 (1.090–1.280)	3.736 (1.040–1.245)	8.79 (1.060–1.27)	p=0.8885
Fibrinogen [mg/dl]	477.231 (322.000–605.000)	528.810 (385.000–623.00)	530.731 (384.000–663.000)	557.85 (441.000–623.000)	p=0.2083
D-dimers [ng/mL]	3424.89 (605.500–1639.50)	3197.286 (590.00–1855.000)	3876.705 (638.500–1716.500)	6033.047 (498.000–2603.000)	p=0.9760
CRP [mg/l]	70.251 (12.850–116.670)#	81.504 (26.960–123.460)^	102.740 (46.570–151.915)	85.113 (35.500–107.855)	p=0.0037
IL-6 [pg/mL]	64.766 (13.330–68.300)*,#	125.416 (22.700–97.500)^	223.128 (36.500–138.900)	214.058 (42.700–144.100)	p=0.0000

Notes: *Statistically significant with MEWS 4 (p=0.03), #Statistically significant with MEWS 3 (p=0.04), ^Statistically significant with MEWS 3 (p=0.001).

Abbreviations: WBC, white blood count; RBC, red blood cells; PLT, platelet count; MPV, mean platelet count; LDH, lactate dehydrogenase; INR, International Normalized Ratio; CRP, C-reactive protein; IL-6, interleukin 6.

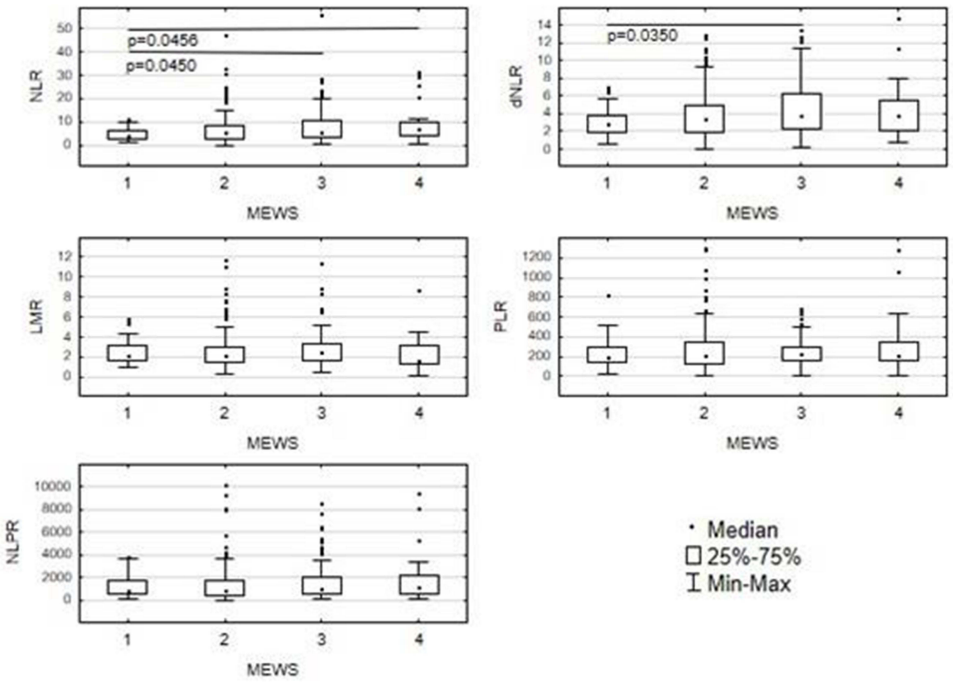

Figure 1 Systemic inflammatory biomarkers ratios in COVID-19 patients according to MEWS classifications.
Abbreviations: NLR, neutrophil/lymphocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; PLR, platelet/lymphocyte ratio; NLPR, neutrophil lymphocyte/platelet ratio.

The value of NLR and dNLR increased significantly with COVID-19 severity. The statistically significant NLR values were recorded between the patients with MEWS 1 and MEWS 3 (p=0.042) and between MEWS 1 and MEWS 4 (p=0.045). The statistically significant dNLR values were recorded between patients with MEWS 1 and MEWS 3 (p=0.035).

Receiver Operating Characteristic (ROC) Curve Analysis of prognostic Factors

ROC analysis demonstrated that NLR, dNLR, and NLPR might be acceptable in the differentiation of severe (MEWS 4) or non-severe (MEWS 1) cases of COVID-19 (Table 5). Therefore, we analyzed the optimal cut-off values calculated using the ROC analysis, and the ROC curves were presented in Figure 2. The areas under the curve (AUC) of NLR, dNLR, and NLPR were 0.589, 0.586, and 0.558. The optimal cut-off values were 3.84, 2.91, and 695.88 for dNLR, NLR, and NLPR. The parameters like LMR and PLR could not be used as potential diagnostic biomarkers for subsequent analysis because their AUC was less than 0.50.

Receiver operating characteristic (ROC) curves of NLR, dNLR, LMR, PLR, and NLPR were created to determine whether the baseline of these biomarkers was predictive of mortality in patients with COVID-19. The AUC values of

Table 4 Comparison of Inflammatory Ratios Between Four Groups of Patients with COVID-19 Divided According to MEWS Classification (Mean Value with Q1–Q3)

COVID-19 Severity (MEWS)	1	2	3	4	Anova Kruskal–Wallis Test
NLR	4.804 (2.735–6.182)*	6.820 (2.732–8.373)	8.087 (3.4647–10.346)	9.456 (4.099–10.018)	p=0.0117
dNLR	3.044 (1.893–3.706)*	3.700 (1.828–4.914)	4.485 (2.303–6.158)	4.221 (2.005–5.559)	p=0.0224
LMR	2.570 (0.280–0.670)	2.630 (1.529–3.024)	4.155 (1.744–3.405)	2.252 (1.264–3.160)	p=0.1940
PLR	238.876 (143.132–298.971)	267.764 (133.835–343.750)	277.590 (154.097–351.753)	294.031 (153.568–353.763)	p=0.9301
NLPR	1242.237 (471.2758–1755.154)	1427.302 (450.7105–1758.522)	1651.623 (598.0003–2004.237)	1875.790 (558.5147–2157.738)	p=0.2940

Abbreviations: NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; NLPR, index of neutrophil-lymphocyte×platelet ratio.

Table 5 Areas Under the Curve (AUC) of NLR, dNLR, LMR, PLR, NLPR and Used to Differentiate Patients with Severe (MEWS 4) and Non-Severe (MEWS 1) COVID-19

Parameter	AUC	p-value	Cut-off	Sensitivity	Specificity	95% Confidence Interval
dNLR	0.586	0.0049	2.91	0.611	0.443	0.526–0.646
NLR	0.589	0.0034	3.84	0.722	0.380	0.530–0.649
LMR	0.517	0.5858	2.72	0.597	0.353	0.455–0.579
PLR	0.518	0.5579	170.98	0.681	0.394	0.458–0.578
NLPR	0.558	0.0501	695.88	0.688	0.430	0.498–0.618

Abbreviations: NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; NLPR, index of neutrophil-lymphocyte×platelet ratio.

NLR, dNLR, and LMR were above 0.6 (Figure 3, Table 6). The optimal cut-off values were as follows: 6.22, 3.52, and 2.06 for dNLR, NLR, and LMR. PLR and NLPR with an AUC value <0.5 and no statistical significance (p>0.05) were excluded.

COX Regression Analysis for Mortality

We performed the COX regression analysis model and Kaplan–Meier curve to identify the possible independent predictors of death during the course of COVID-19. In survival analysis, comorbidities (diabetes, obesity, hypertension, coronary heart failure), age, gender, and SIR biomarkers (NLR, dNLR, LMR, PLR, and NLPR) were analyzed. On admission, our analysis showed that an increase in patients' age (HR 1.072, 95% CI 1.040–1.106), NLR (HR 1.050, 95% CI 1.018–1.083), and LMR (HR 1.021, 95% CI 1.004–1.038) ratio were identified as an independent factor associated with mortality according to multivariate Cox's regression analysis, while other covariates were not (Table 7).

In the analyzed group as a whole, the probability of surviving one week was 0.943 (SE=0.012), two weeks – 0.903 (SE=0.017), three weeks – 0.846 (SE=0.028), and four weeks – 0.779 (SE=0.046).

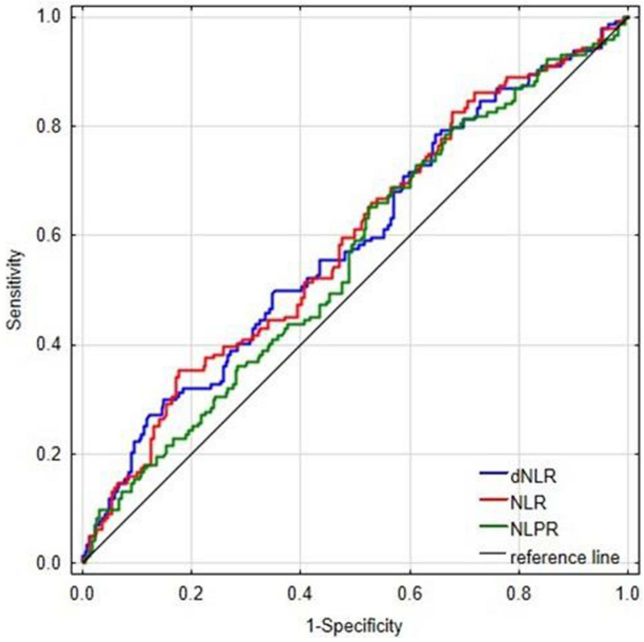

Figure 2 Receiver-operating characteristic (ROC) curves of NLR, dNLR, and NLPR used to differentiate patients with severe and non-severe COVID-19.

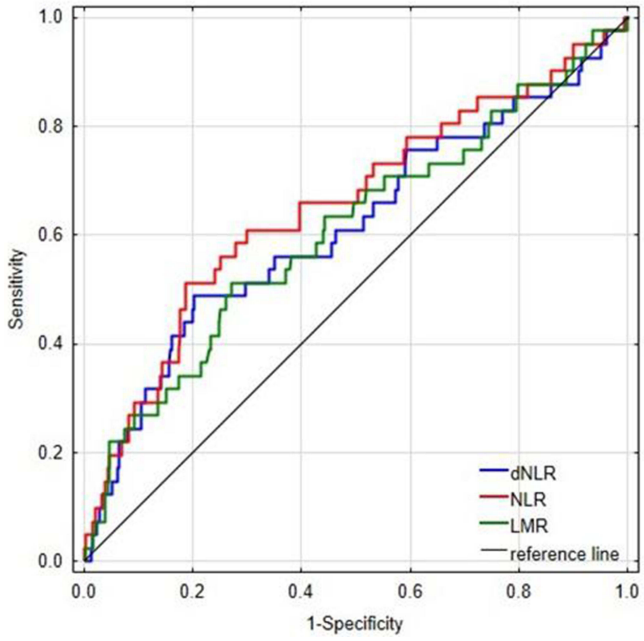

Figure 3 Receiver operating characteristic (ROC) curves of NLR, dNLR, and LMR in predicting death in patients with COVID-19.

Kaplan–Meier analysis was applied to construct a survival curve (Figure 4a–c). In patients over 75 years of age (Figure 4a), NLR median higher than 6.56 (red curve) (Figure 4b), and LMR median lower than 2.23 (blue curve) (Figure 4c), the probability of survival was lower. Kaplan–Meier curve analysis showed that the probability of survival tended to be greater with lower NLR and higher LMR median.

Discussion

Prognostic biomarkers are still necessary for a better understanding of the clinical course and qualifying patients with COVID-19 to the hospital. One of the proposed indicators appears to be NLR, dNLR, PLR, and LMR which correlate with disease severity in several conditions: bacterial and fungal infection, acute stroke, atherosclerosis, cancer, trauma, post-surgery complications, and other condition characterized by tissue damage that activates SIRS (systemic inflammatory response syndrome), eg during COVID-19.[25,26]

The results of our study indicate that NLR, dNLR, and LMR demonstrate clinical implications in the severe course of COVID-19. Generally, in our study of COVID-19 patients, an isolated rise in neutrophil count and consequently, an elevated NLR ratio and dNLR ratio was a significant observation. What is more, these parameters showed an upward tendency with the severity of COVID-19, according to the MEWS classification/score. Other indicators PLR, LMR, and

Table 6 Areas Under the Curve (AUC) of d-NLR, NLR, LMR, PLR, and NLPR in Predicting Death in Patients with COVID-19

Parameter	AUC	p-value	Cut-off	Sensitivity [%]	Specificity [%]	95% Confidence Interval
dNLR	0.615	0.0267	3.52	58	54	0.513–0.717
NLR	0.656	0.0018	6.22	65	60	0.558–0.773
LMR	0.609	0.0329	2.06	63	55	0.509–0.708
PLR	0.580	0.1174	216.80	61	52	0.48–0.68
NLPR	0.585	0.1002	1104	58	54	0.484–0.686

Abbreviations: NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; NLPR, index of neutrophil-lymphocyte×platelet ratio.

Table 7 Multivariable COX Model of Potential Prognostic Variables of Death Associated with Hospital Admission in COVID-19 Patients

Variable	Hazard Ratio (95% CI)	*p* value
Age	1.072 (1.040–1.106)	0.000
NLR	1.050 (1.018–1.083	0.002
LMR	1.021 (1.004–1.038)	0.011
PLR	0.999 (0.998–1.001)	0.907
CRP [mg/L]	1.002 (0.997–1.007)	0.382
IL-6 [pg/mL]	1.000 (0.999–1.000)	0.441
Diabetes mellitus	0.915 (0.607–1.379)	0.672
Hypertension	0.945 (0.471–1.899)	0.876
Obesity	2.147 (0.790–5.835)	0.134
Coronary heart failure	1.085 (0.533–2.206)	0.821
Model stratified by sex		

Abbreviations: NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein; IL-6, interleukin 6.

NLPR also showed an increasing tendency along with the MEWS score, but due to the large diversity of the study group and large standard deviations, these differences were not statistically significant. The most important findings were that hospital mortality was higher among patients with increased NLR median and lower median of LMR.

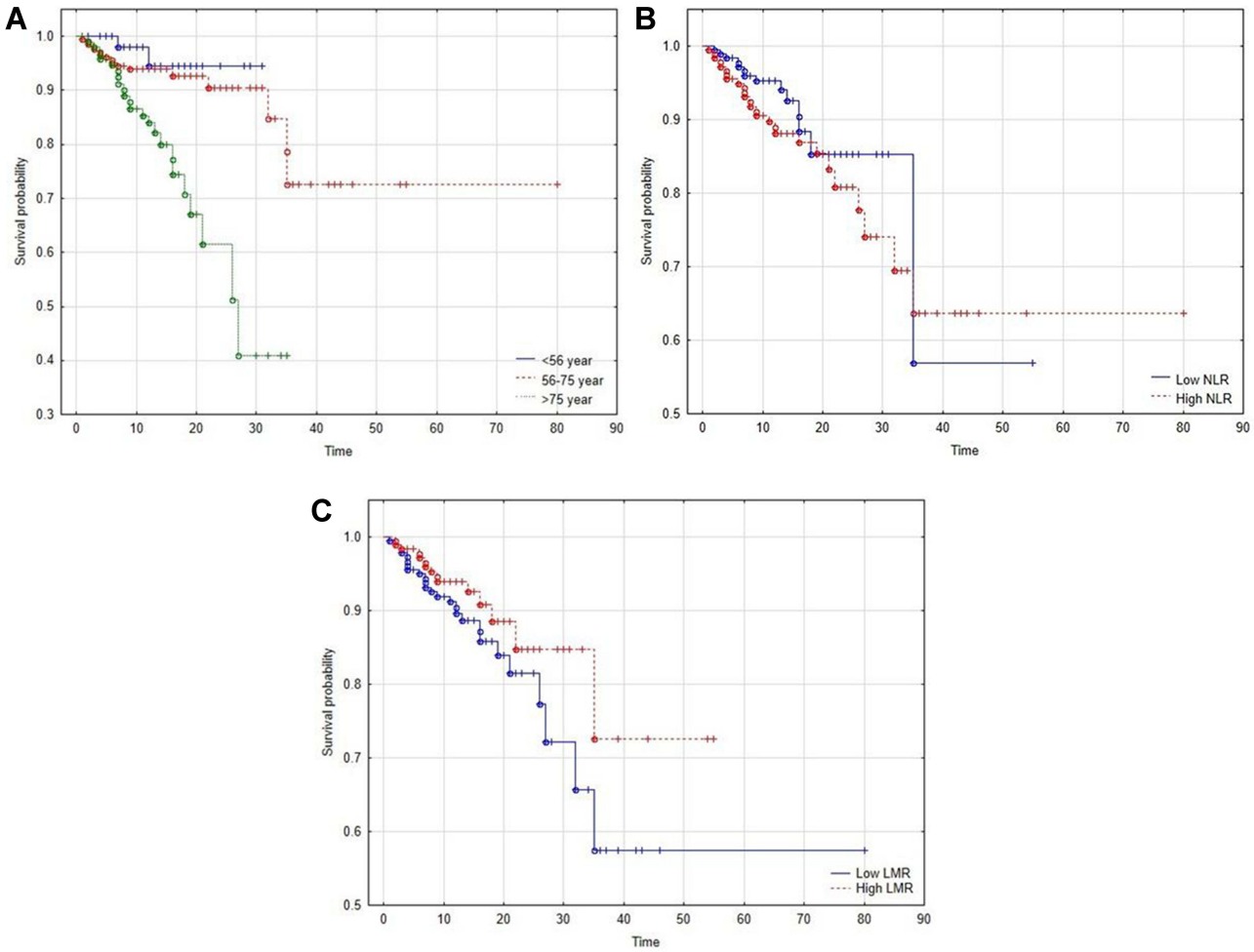

Figure 4 (**a**–**c**) Kaplan-Meier survival curves of patients with COVID-19 according to: (**a**) Age, (**b**) NLR value (median Me = 6.56), (**c**) LMR value (median Me = 2.23).

Among all hematological parameters, NLR seems to be the best biomarker of systemic inflammation intensity in COVID-19 patients. Increasing NLR value was associated with the presence of comorbidities like cardiovascular disease, obesity, and diabetes, which are often associated with the severe course of COVID-19.[27] Our results indicate that NLR may be used to monitor on admission to the hospital or during hospitalization over the course of COVID-19 because a high NLR value potentiates the symptoms' severity and thus mortality rate. NLR is used as one of the variables' prognostic scores. The COVID-GRAM is capable of predicting a risk score based on the outcomes of SARS-CoV-2 infected patients during hospital admission.[28]

Other researchers have also noted elevated levels of NLR, dNLR, and neutrophils, which are the most frequently reported and recognized parameters in the progression of severity and mortality in COVID-19.[22,29,30] NLR, like other ratios (PLR, LMR, NLPR), is widely known as an inexpensive, widely available, and easily measured biomarker obtained in morphology. NLR is a well-known biomarker of infection and systemic inflammation response in COVID-19.[31] The early hyperdynamic phase in SARS-CoV-2 infection is associated with a proinflammatory state, mediated by neutrophils, monocytes, and lymphocytes. Sun et al[32] reported that COVID-19 patients have the lowest lymphocyte count and highest neutrophil count in the severe phase of the disease. In addition, Wang et al[33] showed that several COVID-19 patients have a rising neutrophil count and a failing lymphocyte count during the severe phase. Barnes et al[34] found extensive neutrophil infiltration in pulmonary capillaries in COVID-19 patients. Local production of cytokines and growth factors such as GM-CSF, G-CSF, and M-CSF triggers granulopoiesis which leads to increased production of neutrophils and monocytes at the site of inflammation.[35] Neutrophils, the first cells recruited into the site of inflammation, play a critical role in the elimination of bacteria with specific mechanisms. Neutrophils play a variety of roles during infection. Apart from phagocytosis (also viruses), they can produce and release copious amounts of cytokines to restrict virus replication and can initiate and/or repress adaptive immune processes by promoting bidirectional cross-talk with T-cells.[36,37] Otherwise, neutrophils can also release NETs against viral diseases[38] which may protect the host while the virus recognition mechanism takes place or exacerbate lung hyperinflammation in COVID-19.[39]

Neutrophils up-regulation in patients with COVID-19 is closely associated with lymphopenia,[25] and the rate of this reduction reversely correlates with the severity of COVID-19.[20,40,41] Lymphocyte count was lower in severe and critically ill patients than in normal and mild courses of COVID-19.[2,19] According to Wagner et al[40] observed lymphocytopenia can be an early, useful, and easily obtained prognostic factor determining the clinical course and disease severity in patients admitted to the hospital for COVID-19. In our study group, lymphocyte counts, in accordance with the literature, showed a downward trend with the severity of COVID-19.

The mechanism underlying the reduction in lymphocyte count over the course of the SARS-CoV-2 infection has not yet been identified. Several hypotheses have been proposed to explain lymphopenia during severe COVID-19, including "cytokine storm", T lymphocyte exhaustion, and activation of G-MDCSs, which inhibited T lymphocyte proliferation and suppressed their ability to produce IFN-γ.[35,42,43] Another explanation is that lymphocytes are dominant in the interstitial area of the lung during the SARS-CoV-2 infection.[41] In our study, the percentage of neutrophils was significantly lower in patients with mild COVID-19 (MEWS 1) in comparison to patients with severe COVID-19 (MEWS 3 and 4), who had a higher percentage of neutrophils. Otherwise, we also observed a decreased tendency of lymphocyte percentage in more severe COVID-19 patients than in the mild form of the disease (MEWS 1 vs MEWS 3 $p=0.04$, and MEWS 1 vs MEWS 4 $p= 0.03$) (data not presented).

The main problem is the lack of unified cut-off values or reference ranges for the ratios, also there are no cut-off values for prognostic prediction which vary across several studies. The discrepancies are associated with race and heterogeneity of the tested population. In most studies, the normal value of NLR in healthy subjects is usually reported at approximately 1–3,[44] critically ill patients have higher NLR as compared to non-ICU patients.[32] The highest NLR cut-off was observed in patients with sepsis and septic shock. Dragonescu et al[44] observed NLR values between 9.5 and 10.3 in these patients, suggesting the potential value of NLR in assessing the severity of sepsis, whereas in patients with COVID-19 NLR values also differ among the patient's population and ethnic groups. The highest NLR ratio associated with higher mortality was observed by Al-Mazedi et al.[45] They found that in patients with NLR>9, the fatality of SARS-CoV -2 was 25 times higher than in patients with NLR<9. According to Liu et al[9], an NLR value >3.3 was associated independently with more severe COVID-19 and with lower survival. In another study, NLR >3.13 was an independent

risk factor for severe COVID-19.[46] Li et al[47] show in meta-analysis that more than half of the included studies used cut-off value greater than 6.5 for the mortality. So, we can conclude, that NLR evaluation could allow for an earlier diagnosis of severe cases which may reduce the overall mortality of COVID-19.

Our data are in line with the previous studies on the subject. We indicated that the cut-off values for NLR and dNLR in differentiation between severe and non-severe patients were 3.8 and 2.9 (respectively), while in high risk of mortality, the cut-off value for NLR and dNLR was much higher (6.2 and 3.5, respectively). The AUC under the ROC curve was also higher in predicting the death of patients with COVID-19 with values for NLR and dNLR at 0.656, 0.615, respectively, than in differentiating patients with severe vs non-severe courses of COVID-19 (0.589, 0.586). Our results indicate that NLR and dNLR have better diagnostic power in predicting death in patients with COVID-19. As we presented in our review, the NLR area under the ROC curve differs from many studies, eg Wang et al[33] observed AUC=0.963, while Seyit et al[30] closed to our values - 0.615.[17] Some authors indicate that LMR could also be used as a novel inflammatory biomarker that can predict the severity of COVID-19.[48,49] In our study, the AUC for LMR was acceptable (0.609) in predicting death with the cut-off =2.06.

Potential prognostic factors for mortality in COVID-19 were analyzed with the use of multivariable logistic regression. In our study, 43 (12%) patients died during hospitalization. These data are consistent with those of other studies, which reported that even 15–17% of patients died during hospitalization.[23,50] Our analysis revealed a significant effect of NLR, LMR, and age on mortality in patients with COVID-19. The results indicated that NLR median value higher than 5.56 and LMR lower than 2.23 calculated on admission were two independent prognostic factors in identifying critically ill COVID-19 patients with a high risk of death. The mortality rate was also higher in older patients (>75 years old). It is commonly known that older people are generally at higher risk of getting COVID-19, moreover they also have a higher risk of severe illness and death from COVID-19.[51,52] These data are consistent with other published studies which reported an association between age and NLR with a severe course of COVID-19.[51,53–55] Elevated NLR value is associated with chronic diseases and comorbidities, such as hypertension, cardiovascular diseases, obesity, and diabetes which correlate with a severe course of COVID-19.[53] Our study indicates that apart from NLR and LMR, age is a very important variable associated with high risk of death in COVID-19 patients. The intensity of the immunological response was related to the severity of infection, and both of them are associated with a less favorable prognosis. NLR and PLR can be utilized as a biomarker for earlier use in the diagnostic process of severe cases which may reduce the mortality of COVID-19. According to Pimental et al,[53] NLR and LMR should be used for monitoring during hospitalization, because of their high value in predicting the severity of the symptoms and thus the mortality.

Our study was conducted on a relatively large group of patients with various clinical courses, but there are limitations to it. The main limitation of our retrospective study is the fact that our patients were admitted to one center (Temporary Hospital for COVID-19) and were mostly in mediocre condition. When a study is designed in a single center of COVID-19, unit selection bias may be inevitable and some patient data is unrecoverable. Like in other studies, we could not exclude the possible influence of some treatment before hospitalizing on the peripheral blood-based biomarkers.

Improving laboratory diagnostics in the course of COVID-19 is an important element of effectively combating the severe course of SARS-CoV-2 infection. It is the key to reducing the severe course and risk of death and introducing a faster, more effective treatment. Identifying factors and laboratory tests related to a severe course and mortality is very important in the quick identification of patients requiring hospitalization and intensive care. Peripheral blood combinations of biomarkers that reflect inflammatory status may be a good alternative in this regard, especially since they can be obtained quickly and cheaply. In conclusion, our results indicate that NLR and dNLR may help quickly identify high-risk groups of patients with a more severe course of COVID-19 on admission to the hospital. Among all clinically studied factors only, the NLR and the LMR ratios were independently and precisely associated with mortality in COVID-19 during hospitalization and could be used as prognostic biomarkers.

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Disclosure

All authors declare that there is no possible conflict of interest in this work.

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