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REVIEW

The Prognostic Role of Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, and Platelet-to-Lymphocyte Ratio in the Risk of Major Adverse Cardiovascular Events and Mortality in Patients with COVID-19: a State-of-the-Art Review

Eliza Mihaela Arbănași[1], Eliza Russu[2,3]

[1] Doctoral School of Medicine and Pharmacy, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[2] Clinic of Vascular Surgery, Emergency County Hospital, Târgu Mureș, Romania
[3] Department of Vascular Surgery, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania

ABSTRACT

Coronavirus disease (COVID-19) is a viral infection caused by SARS-CoV-2 that has become a global health emergency with a negative impact on patient care. The evolution of patients with COVID-19 is unpredictable, with an unfavorable evolution in the case of patients with comorbidities. This state-of-the-art review focuses on the role of hematological inflammatory biomarkers: the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in predicting major adverse cardiovascular events (MACE) and mortality in patients with COVID-19. In this review, we included 21 studies that investigated the role of biomarkers in the risk of mortality and MACE, reporting on a total of 7,588 patients. Regarding the clinical data, 57.49% of the patients presented hypertension (15 out of the 21 studies reported hypertensive patients), followed by ischemic heart disease in 33.56% of patients (13 studies) and diabetes in 30.37% of patients (17 studies). In additional, among the usual risk factors, 23.55% of patients presented obesity (7 studies) and 23.02% were active smokers (10 studies). We recorded an average cut-off value of 7.728 for NLR (range 2.6973–15.2), 0.594 for MLR (range 0.26–0.81), and 215.07 for PLR (range 177.51–266.9) for the risk of MACE and mortality. We also recorded an average area under the curve (AUC) of 0.783 for NLR, 0.744 for MLR, and 0.713 for PLR. Our findings suggest that these biomarkers exhibit prognostic value in predicting adverse outcomes, and that evaluating these biomarkers at admission could provide novel information in stratifying risk groups for improving patient management.

Keywords: COVID-19, inflammatory biomarkers, mortality, outcome

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CORRESPONDENCE

Eliza Mihaela Arbănași
Str. Gheorghe Marinescu nr. 38
540142 Târgu Mureș, Romania
Tel: +40 740 974 049
Email: arbanasi.eliza@gmail.com

INTRODUCTION

Coronavirus disease (COVID-19) has spread globally since 2020, with over 750 million confirmed cases and approximately 7 million fatalities.[1] COVID-19 is an infectious illness with a wide spectrum of clinical signs, ranging from asymptomatic to moderately symptomatic and severe forms. This indicates that the host response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a significant role.[2,3] The COVID-19 pandemic has also negatively affected hospitals' activity regarding chronic pathology and elective surgery.[4,5]

Studies have found the majority of infections caused by SARS-CoV-2 to be moderate; 31% were severe (with dyspnea, hypoxia, or more than 50% lung involvement on detection imaging), whereas 5% of patients developed a life-threatening condition with respiratory failure or multiple organ dysfunction.[6] The risk of mortality from COVID-19 is heavily influenced by age and medical history. Older individuals are considerably more likely to have catastrophic or fatal illness outcomes, particularly if they have comorbidities such as hypertension, cardiovascular disease, obesity, chronic renal disease, pulmonary disease, and diabetes.[3,7,8]

Researchers have used specific ratios to identify and analyze several inflammatory disorders in recent years. Numerous investigations have discovered that various combinations of hematological elements of the systemic immune response, such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), were successful indicators of prognosis in patients with an array of malignancies, heart disease, diabetes, acute ischemic stroke, peripheral arterial disease, and chronic kidney disease.[9–19] The elements of these simply derived metrics are widely available, affordable, and frequently assessed as part of a complete blood test report in everyday practice. Calculating these hematological components associated with the systemic immune response may offer healthcare specialists an additional helpful tool for clinical risk classification.

Our study aims to provide an updated overview of the current landscape of the role of hematological inflammatory biomarkers (NLR, MLR, and PLR) on the risk of developing major adverse cardiovascular events (MACE) and mortality in patients with COVID-19, focusing on the optimal cut-off value of the biomarkers, their clinical impact, and the possibility of stratification of groups of patients at risk.

Following the analysis of the studies published in the literature, we included 21 articles in this review, reporting on a total number of 7,588 patients. The average age of the patients was 65.36 years, and 56.57% were male. Regarding the clinical data, 57.49% of the patients presented hypertension (15 out of the 21 studies reported hypertensive patients), followed by ischemic heart disease in 33.56% of patients (13 studies) and diabetes in 30.37% of patients (17 studies). In additional, among the usual risk factors, 23.55% of patients presented obesity (7 studies), and 23.02% were active smokers (10 studies). Regarding the hematological inflammatory biomarkers, NLR was analyzed in 21 studies, PLR was investigated in nine studies, and MLR was explored in only six. The rest of the data are shown in Table 1.

NLR

Regarding mortality, we identified an average NLR of 9.24 (range 5.00–17.70) in the group of patients with negative outcomes, much higher than in the control group, in which the average NLR was 4.86 (range 2.14–12.29). In addition, in 14 studies, the authors identified an optimal cut-off value of 7.16 (range 2.70–15.20) using receiver operating characteristic (ROC) analysis. The area under the curve (AUC) analysis yielded an average value of 0.77 (range 0.63–0.87), with an average sensitivity of 72.54% and a specificity of 72.31% (Figure 1 and Table 2). When analyzing the prognostic role of NLR in MACE, we found an optimal average cut-off value of 9.43 (range 5.40–13.67), with an average AUC of 0.830, a sensitivity of 76.87%, and a specificity of 82.2% (Table 2).

Abrishami *et al.*,[20] Pakos *et al.*,[21] Allahverdiyev *et al.*,[22] and Zeng *et al.*[23] found that NLR is associated with mortality, with odd ratios (ORs) and hazard ratios (HRs) ranging from 1.03 to 5.40 and 95% confidence intervals (CIs) ranging from 1.00 to 21.20. In addition, Rose *et al.*,[24] Halmaciu *et al.*,[25] Arbănași *et al.*,[26] Mureșan *et al.*,[27] and Citu *et al.*[28] found significantly higher OR/HR values, ranging from 13.07 to 24.13, with tight confidence intervals. Furthermore, Ghobadi *et al.*,[29] Regolo *et al.*,[30] Seyfi *et al.*,[31] Zhan *et al.*,[32] and Predenciuc *et al.*[33] emphasize the relationship between NLR and MACE. Regarding the Kaplan–Meier survival analysis, Fois *et al.*,[34] Zeng *et al.*,[23] Citu *et al.*,[28] Ghobadi *et al.*,[29] Regolo *et al.*,[30] and Zhan *et al.*[32] found a statistically significant difference for the primary endpoint based on the cut-off value (Table 3).

MLR

The MLR, derived from the absolute monocyte and lymphocyte counts, is another inflammatory biomarker with a prognostic role in the negative evolution of patients with numerous pathologies. According to studies done in Italy

TABLE 1. General characteristics of the studies included in the analysis

Study	Patients, *n*	Mean age, years	Male sex, *n* (%)	Hypertension, *n* (%)	Ischemic heart disease, *n* (%)	Diabetes, *n* (%)	Obesity, *n* (%)	Active smoking, *n* (%)	Observation
Fois *et al.*[34]	119	72	77 (64.7%)	–	–	25 (21%)	27 (22.69%)	36 (30.25%)	NLR, MLR, and PLR
Abrishami *et al.*[20]	100	55.5	68 (68%)	33 (33%)	21 (21%)	21 (21%)	25 (25%)	–	NLR and PLR
Pakos *et al.*[21]	242	66.03	208 (85.95%)	180 (74%)	–	118 (49%)	–	–	NLR
Allahverdiyev *et al.*[22]	455	56	217 (47.7%)	170 (37.4%)	88 (19.3%)	128 (28.1%)	–	–	NLR
Zeng *et al.*[23]	352	>60 years 133 (37.78%) <60 years 219 (62.22%)	190 (53.97%)	–	–	–	–	57 (16.19%)	NLR
Moradi *et al.*[36]	219	–	137 (62.6%)	85 (38.8%)	46 (21%)	83 (38%)	–	23 (10.5%)	NLR
Yildiz *et al.*[37]	198	Derivation group 64.4	110 (55%)	101 (51%)	107 (54%)	49 (25%)	–	8 (4%)	NLR
		Validation group 65	65 (64%)	52 (51.5%)	45 (44.6%)	22 (21.8%)	–	2 (2%)	
Karaaslan *et al.*[38]	191	54.32	94 (49.2%)	72 (37.7%)	–	44 (23%)	–	–	NLR and PLR
Kudlinski *et al.*[39]	285	62	189 (66.3%)	153 (55.2%)	26 (9.4%)	57 (20.7%)	134 (47.7%)	20 (7%)	NLR
Rose *et al.*[24]	454	–	291 (64.1%)	225 (49.6%)	137 (30.2%)	119 (26.2%)	103 (22.7%)	–	NLR and PLR
Halmaciu *et al.*[25]	267	71.19	159 (59.55%)	167 (62.55%)	145 (54.31%)	116 (43.45%)	69 (25.84%)	99 (37.08%)	NLR and MLR
Arbănași *et al.*[26]	510	69.6	247 (62.37%)	228 (57.78%)	138 (34.85%)	150 (37.88%)	114 (28.79%)	134 (33.84%)	NLR, MLR, and PLR
Mureșan *et al.*[27]	889	70.5	474 (53.32%)	735 (82.67%)	513 (57.70%)	268 (30.14%)	146 (16.42%)	256 (28.79%)	NLR, MLR, and PLR
Citu *et al.*[28]	108	63.31	56 (51.9%)	76 (70.4%)	51 (47.2%)	50 (46.3%)	–	–	NLR, MLR, and PLR
Ghobadi *et al.*[29]	1,792	Elderly 76.29 Non-elderly 48.35	988 (55.13%)	–	–	522 (29.12%)	–	–	NLR, MLR, and PLR
Regolo *et al.*[30]	411	72	237 (57.7%)	244 (59.4%)	70 (17.1%)	111 (27%)	–	–	NLR
Seyfi *et al.*[31]	312	–	–	–	–	–	–	–	NLR
Strazzulla *et al.*[35]	184	–	103 (55.97%)	–	–	–	–	–	NLR and PLR
Zhan *et al.*[32]	159	–	73 (45.91%)	72 (45.28%)	15 (9.43%)	33 (20.75%)	–	53 (33.33%)	NLR
Predenciuc *et al.*[33]	130	71	86 (66.2%)	117 (90%)	106 (81.5)	39 (30%)	–	–	NLR
Khorvash *et al.*[40]	211	66.28	110 (52.13%)	126 (59.7%)	53 (25.1%)	103 (48.8%)	–	–	NLR

TABLE 2. NLR studies and predictive values for clinical outcomes

Study	Year	Country	Biomarker	Study group value	Control group value	Cut-off value	AUC ROC analysis	Sensitivity (%)	Specificity (%)	Outcome
Fois *et al.*[34]	2020	Italy	NLR	9.17	5	15.2	0.697	38%	97%	Mortality
Abrishami *et al.*[20]	2020	Iran	NLR	5.02	3.02	3.65	0.678	62.5%	60%	Mortality
Pakos *et al.*[21]	2020	USA	NLR	6.4	4.5	–	–	–	–	Mortality
Allahverdiyev *et al.*[22]	2020	Turkey	NLR	12.1	3.2	3	0.842	92%	53%	Mortality
Zeng *et al.*[23]	2021	China	NLR	5.33	2.14	2.6937	0.828	92.9%	63.9%	Mortality
Moradi *et al.*[36]	2021	Iran	NLR	5	4.1	3.3	–	–	–	Mortality
Yildiz *et al.*[37]	2021	Belgium	NLR	–	–	5.94	0.665	62%	64%	Mortality
Karaaslan *et al.*[38]	2022	Turkey	NLR	9.27	2.73	4.21	0.810	77.1%	73.7%	Mortality
Kudlinski *et al.*[39]	2022	Poland	NLR	17.7	12.29	11.57	0.629	63%	60.5%	Mortality
Rose *et al.*[24]	2022	Switzerland	NLR	8.2	5.0	–	–	–	–	Mortality
Halmaciu *et al.*[25]	2022	Romania	NLR	11.04	3.73	6.97	0.869	80.5%	85.4%	Mortality
Arbănași *et al.*[26]	2022	Romania	NLR	8.45	3.01	4.57	0.845	86.6%	72%	Mortality
Mureșan *et al.*[27]	2022	Romania	NLR	9.74	5.38	9.4	0.868	81.8%	74.4%	Mortality
Citu *et al.*[28]	2022	Romania	NLR	13.83	8.31	9.1	0.689	70%	67%	Mortality
Ghobadi *et al.*[29]	2022	Iran	NLR	6.07	4.7	9.38	0.817	73.3%	86.5%	Mortality
Regolo *et al.*[30]	2022	Italy	NLR	–	–	11.38	0.772	72.9%	71.9%	Mortality
Seyfi *et al.*[31]	2023	Iran	NLR	11.3	5.8	7.02	0.760	63%	83%	Mortality
						MACE				
Strazzulla *et al.*[35]	2021	France	NLR	7.5	3.2	–	–	–	–	Acute pulmonary embolism
Zhan *et al.*[32]	2021	China	NLR	16.28	4.75	10.14	0.803	81.2	82.6	MACE
Arbănași *et al.*[26]	2022	Romania	NLR	–	–	8.34	0.882	81.6%	87.4%	Acute limb ischemia
Mureșan *et al.*[27]	2022	Romania	NLR	–	–	9.63	0.836	77%	77.8%	Deep vein thrombosis
Mureșan *et al.*[27]	2022	Romania	NLR	–	–	13.67	0.801	67.7%	81%	Acute pulmonary embolism
Predenciuc *et al.*[33]	2022	Republic of Moldova	NLR	11.1	6.3	5.4	–	–	–	Major amputation or mortality
Khorvash *et al.*[40]	2022	Iran	NLR	13.9	8.03	–	–	–	–	Acute ischemic stroke

TABLE 3. The association between NLR and clinical outcomes: ORs, HRs, and survival analyses

Study	Biomarker	OR/HR	95% CI		p value	Outcome	Kaplan–Meier survival analysis	log rank p value
			Lower	Upper				
Fois *et al.*[34]	NLR	1.02	0.99	1.06	0.10	Mortality	In-hospital mortality based on cut-off value	<0.001
Abrishami *et al.*[20]	NLR	1.124	1.01	1.25	0.036	Mortality	–	–
Pakos *et al.*[21]	NLR	1.038	1.003	1.074	0.031	Mortality	–	–
Allahverdiyev *et al.*[22]	NLR	1.261	1.054	1.509	0.011	Mortality	–	–
Zeng *et al.*[23]	NLR	5.4 21.2 19.8	2.6 2.8 2.6	11.1 161.3 151.4	<0.001	Mortality	Disease deterioration based on cut-off value	<0.001
Moradi *et al.*[36]	NLR	1.03	1.003	1.07	0.03	Mortality	One-month mortality based on cut-off value	0.16
Rose *et al.*[24]	NLR	1.82	1.14	2.95	0.013	Mortality	–	–
Halmaciu *et al.*[25]	NLR	24.13	12.2	47.73	<0.001	Mortality	–	–
Arbănași *et al.*[26]	NLR	16.32	9.09	29.3	<0.001	Mortality	–	–
Mureșan *et al.*[27]	NLR	13.07	8.29	20.62	<0.001	Mortality	–	–
Citu *et al.*[28]	NLR	3.85	1.35	10.95	0.01	Mortality	In-hospital mortality based on cut-off value	<0.001
Ghobadi *et al.*[29]	NLR	3.57	2.859	4.458	<0.0001	Mortality	In-hospital mortality based on cut-off value for non-elderly and elderly	<0.001 / <0.001
Regolo *et al.*[30]	NLR	1.62	–	–	<0.0001	Mortality	In-hospital mortality based on tertiles	<0.0001
Seyfi *et al.*[31]	NLR	1.121	1.072	1.179	<0.0001	Mortality	–	–
Zhan *et al.*[32]	NLR	2.24	1.49	4.47	<0.001	MACE	6-month MACE based on cut-off value	0.010
Arbănași *et al.*[26]	NLR	30.28	13.97	65.6	<0.001	Acute limb ischemia	–	–
Mureșan *et al.*[27]	NLR	11.7	7.99	17.13	<0.001	Deep vein thrombosis	–	–
Mureșan *et al.*[27]	NLR	10.5	5.86	18.8	<0.001	Acute pulmonary embolism	–	–
Predenciuc *et al.*[33]	NLR	2.46	1.0	6.03	0.04	Major amputation or mortality	–	–

TABLE 4. MLR studies and predictive values for clinical outcomes

Study	Year	Country	Patients, *n*	Biomarker	Study group value	Control group value	Cut-off value	AUC ROC analysis	Sensitivity (%)	Specificity (%)	Outcome
Fois *et al.*[34]	2020	Italy	119	MLR	0.429	0.333	0.364	0.617	69%	57%	Mortality
Halmaciu *et al.*[25]	2022	Romania	267	MLR	0.75	0.33	0.54	0.826	74.4%	81.6%	Mortality
Arbănași *et al.*[26]	2022	Romania	510	MLR	0.62	0.32	0.45	0.758	68.4%	74%	Mortality
Mureșan *et al.*[27]	2022	Romania	889	MLR	1.14	0.47	0.78	0.794	71.3%	74%	Mortality
Citu *et al.*[28]	2022	Romania	108	MLR	0.83	0.53	0.69	0.661	58%	74%	Mortality
Ghobadi *et al.*[29]	2022	Iran	1,792	MLR	0.20	0.16	0.26	0.628	59.4%	62.4%	Mortality
						MACE					
Arbănași *et al.*[26]	2022	Romania	510	MLR	–	–	0.49	0.787	71.4%	71.6%	Acute limb ischemia
Mureșan *et al.*[27]	2022	Romania	889	MLR	–	–	0.78	0.824	77%	76.2%	Deep vein thrombosis
Mureșan *et al.*[27]	2022	Romania	889	MLR	–	–	0.81	0.766	71%	72.1%	Acute pulmonary embolism

TABLE 5. The association between MLR and clinical outcomes: ORs, HRs, and survival analyses

Study	Biomarker	OR/HR	95% CI		p value	Outcome	Kaplan–Meier survival analysis	log rank p value
			Lower	Upper				
Fois *et al.*[34]	MLR	1.60	0.62	4.09	0.32	Mortality	In-hospital mortality based on cut-off value	0.006
Halmaciu *et al.*[25]	MLR	6.49	2.51	22.24	<0.001	Mortality	–	–
Arbănași *et al.*[26]	MLR	5.51	3.50	8.67	<0.001	Mortality	–	–
Mureșan *et al.*[27]	MLR	6.89	4.64	10.23	<0.001	Mortality	–	–
Citu *et al.*[28]	MLR	3.05	1.16	8.05	0.02	Mortality	In-hospital mortality based on cut-off value	<0.001
Ghobadi *et al.*[29]	MLR	1.502	1.212	1.86	<0.0001	Mortality	In-hospital mortality based on cut-off value for non-elderly and elderly	<0.001
Arbănași *et al.*[26]	MLR	6.82	3.51	13.28	<0.001	Acute limb ischemia	–	–
Mureșan *et al.*[27]	MLR	11.19	7.68	16.29	<0.001	Deep vein thrombosis	–	–
Mureșan *et al.*[27]	MLR	8.96	5.11	15.69	<0.001	Acute pulmonary embolism	–	–

TABLE 6. PLR studies and predictive values for clinical outcomes

Study	Year	Country	Patients, *n*	Biomarker	Study group value	Control group value	Cut-off value	AUC ROC analysis	Sensitivity (%)	Specificity (%)	Outcome
Fois *et al.*[34]	2020	Italy	119	PLR	265	214	240	0.572	59%	58%	Mortality
Abrishami *et al.*[20]	2020	Iran	100	PLR	202	160.8	–	0.559	–	–	Mortality
Karaaslan *et al.*[38]	2022	Turkey	191	PLR	287.5	139.94	189.5	–	–	–	Mortality
Rose *et al.*[24]	2022	Switzerland	454	PLR	268.3	215.5	–	–	–	–	Mortality
Arbănași *et al.*[26]	2022	Romania	510	PLR	229.83	128.22	177.51	0.775	68.4%	77.5%	Mortality
Mureșan *et al.*[27]	2022	Romania	889	PLR	363.16	156.22	266.9	0.819	72%	81.1%	Mortality
Citu *et al.*[28]	2022	Romania	108	PLR	345	324	–	–	–	–	Mortality
Ghobadi *et al.*[29]	2022	Iran	1,792	PLR	168	154	230	0.585	52.6%	63.1%	Mortality
						MACE					
Strazzulla *et al.*[35]	2021	France	184	PLR	259	204	–	–	–	–	Acute pulmonary embolism
Arbănași *et al.*[26]	2022	Romania	510	PLR	–	–	178.99	0.858	81.6%	73.1%	Acute limb ischemia
Mureșan *et al.*[27]	2022	Romania	889	PLR	–	–	230.67	0.802	72.8%	76.8%	Deep vein thrombosis
Mureșan *et al.*[27]	2022	Romania	889	PLR	–	–	207.06	0.734	74.2%	61.3%	Acute pulmonary embolism

TABLE 7. The association between PLR and clinical outcomes: ORs, HRs, and survival analyses

Study	Biomarker	OR/HR	95% CI		p value	Outcome	Kaplan–Meier survival analysis	log rank p value
			Lower	Upper				
Fois *et al.*[34]	PLR	1.0006	1.00	1.0013	0.058	Mortality	In-hospital mortality based on cut-off value	0.13
Rose *et al.*[24]	PLR	1.37	0.79	2.46	0.27	Mortality	–	–
Arbănași *et al.*[26]	PLR	7.47	4.71	11.83	<0.001	Mortality		
Mureșan *et al.*[27]	PLR	11.04	7.34	16.62	<0.001	Mortality		
Ghobadi *et al.*[29]	PLR	1.451	1.17	1.799	<0.0001	Mortality	In-hospital mortality based on cut-off value for non-elderly and elderly	<0.001 / 0.10
Arbănași *et al.*[26]	PLR	12.07	7.71	21.77	<0.001	Acute limb ischemia	–	–
Mureșan *et al.*[27]	PLR	8.36	5.82	12.02	<0.001	Deep vein thrombosis	–	–
Mureșan *et al.*[27]	PLR	6.26	3.54	11.07	<0.001	Acute pulmonary embolism	–	–

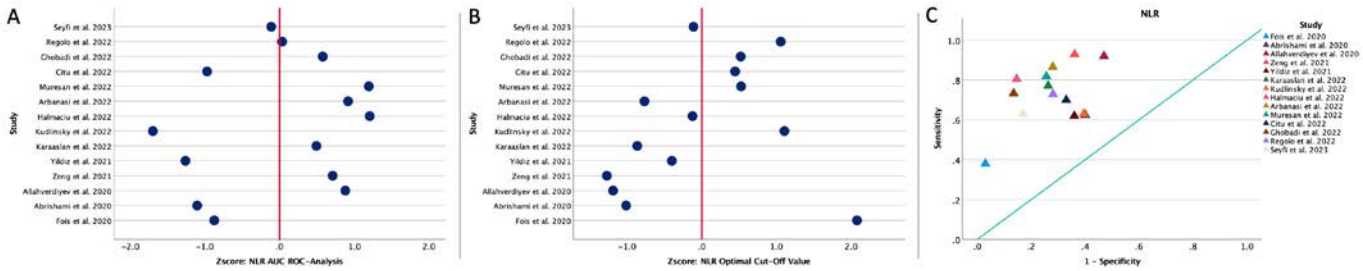

FIGURE 1. **A**, ROC analysis and AUC for NLR regarding mortality. Values are expressed per 1 s.d. increase regarding the median value. **B**, Distribution of the optimal cut-off values for NLR regarding mortality. Values are expressed per 1 s.d. increase regarding the median value. **C**, The position of the optimal cut-off value depending on the sensitivity and specificity of each value, regarding mortality.

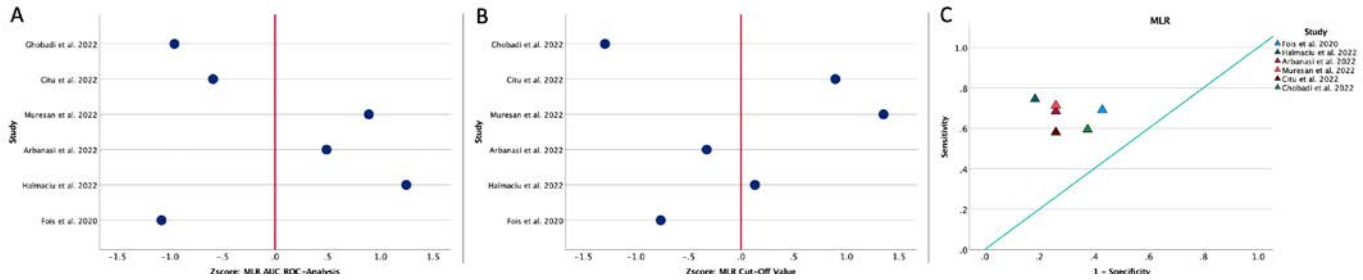

FIGURE 2. **A**, ROC analysis and AUC for MLR regarding mortality. Values are expressed per 1 s.d. increase regarding the median value. **B**, Distribution of the optimal cut-off values for MLR regarding mortality. Values are expressed per 1 s.d. increase regarding the median value. **C**, The position of the optimal cut-off value depending on the sensitivity and specificity of each value, regarding mortality.

and Iran by Fois *et al.*[34] and Ghobadi *et al.*[29], MLR biomarker levels range between 0.364 and 0.628, with specificities between 57% and 62.4%. In comparison, research done by Halmaciu *et al.*,[25] Arbănași *et al.*,[26] Mureșan *et al.*,[27] and Citu *et al.*[28] in Romania shows better ROC analysis and AUC values (between 0.661 and 0.826) and more consistent specificities (between 74% and 81.6%) in connection to mortality. Arbănași *et al.*[26] and Mureșan *et al.*[27] present essential information for acute limb ischemia, deep vein thrombosis, and acute pulmonary embolism, with remarkable specificities ranging from 71.6% to 76.2%. This investigation reveals that MLR may be a potential biomarker, particularly when evaluating the risk of mortality and MACE, with a focus on the specificity achieved in recent Romanian investigations.

We found a cut-off value of 0.516 (range 0.26–0.83), with an AUC of 0.71 (range 0.62–0.83), sensitivity of 66.75% (range 58.00–74.4%) and specificity of 70.50% (range 57.00–81.60%) in terms of mortality (Figure 2 and Table 4).

Regarding mortality, Halmaciu *et al.*[25] discovered a significant association between MLR and mortality, with an OR of 6.49 (95% CI 2.51–22.24, $p < 0.001$), whereas Ghobadi *et al.*[29] discovered a strong association, with an OR of 1.50 (95% CI 1.21–1.86, $p < 0.0001$). Furthermore, Arbănași *et al.*[26] and Mureșan *et al.*[27] reported substantial associations between MLR and various vascular diseases, including acute limb ischemia and deep vein thrombosis, with ORs and HRs underlining the biomarker's influence in these conditions. However, we must highlight the diversity in the definition of outcomes and the cut-off values used because they may contribute to considerable discrepancies in research results. Hence, methodological standardization is essential for facilitating inter-study comparisons and validating the relevance of MLR in prognostic evaluation in various medical scenarios. Regarding the Kaplan–Meier survival analysis, only Fois *et al.*,[34] Citu *et al.*,[28] and Ghobadi *et al.*[29] have identified a statistically significant difference in in-hospital mortality based on the cut-off value of MLR ($p < 0.05$ for all) (Table 5).

PLR

We found eight studies that analyzed the prognostic role of PLR regarding mortality. The average value of PLR was 254.82 (range 168.00–363.16) in the case of patients with a negative outcome and 166.95 (range 128.22–215.50) for the control group. In addition, eight studies presented the results of the ROC analysis, in which we identified an average AUC value of 0.66 (range 0.56–0.82) and an optimal calculated cut-off value of 220.78 (range 177.51–266.90),

with a sensitivity of 63.00% (range 52.60–72.00%) and a specificity of 69.92% (range 58.00–81.10%) (Table 6). Also, Strazzulla *et al.*,[35] Arbănași *et al.*,[26] and Mureșan *et al.*[27] demonstrated a positive association between high PLR values and the risk of MACE.

Regarding the predictive role of PLR in clinical outcomes, Fois *et al.*[34] and Rose *et al.*[24] found no statistically significant associations between PLR and mortality. However, Arbănași *et al.*,[26] Mureșan *et al.*,[27] and Ghobadi *et al.*[29] reported a positive association between high baseline values of PLR and mortality. In addition, Arbănași *et al.*[26] discovered a correlation between PLR and acute limb ischemia, whereas Mureșan *et al.*[27] discovered correlations between PLR and deep vein thrombosis and acute pulmonary embolism. Differences in ORs, CIs, and p values between studies highlight the heterogeneity of results and suggest that a rigorous and in-depth review of study techniques and populations is needed to clarify the correlation between PLR and various clinical outcomes. Nevertheless, Ghobadi *et al.*[29] found a significant difference in the Kaplan–Meier survival analysis based on the cut-off value of PLR for non-elderly patients ($p < 0.001$) but not for the elderly ($p = 0.10$) (Table 7).

CONCLUSIONS

Based on the results of our state-of-the-art review, we can conclude that NLR, MLR, and PLR have good predictive values regarding the risk of MACE and mortality in patients with COVID-19. The evaluation of hematological inflammatory biomarkers at admission, in the case of patients with viral or septic infections, could help in the stratification of risk groups for better management.

CONFLICT OF INTEREST

Nothing to declare.

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