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D-NLR, and neutrophil count as early predictive biomarkers of disease severity and poor disease outcome in SARS-CoV-2 infected patients from Kashmir

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Abstract

Background: The complete blood count (CBC) profile has been found extremely useful in monitoring the growth of SARS-CoV-2 infection; however, predictive CBC parameters that could be used in the management of the disease may vary in different populations.

Methods: This study comparatively analyzed the CBC profile of SARS-CoV-2 patients (N=75; confirmed positive by real-time polymerase chain reaction [PCR]) and healthy individuals (confirmed negative by real-time PCR) from Kashmir (North India).

Results: Compared with healthy individuals, most of the CBC parameters (hemoglobin levels [13.43 vs 10.9 g/dL; P = 0.0001], lymphocytes [16.04% vs 30.8%; P = 0.00001], monocytes [5.53% vs 7.53%; P = 0.009], and platelet count [150 vs 186 ×103 µL; P = 0.037]) were significantly low in SARS-CoV-2 infected patients, while neutrophilia was more common in infected patients (76.77% vs 59.26%). Among derived parameters, the neutrophil-to-lymphocyte ratio (NLR; 7.31 vs 2.04; P = 0.001) and derived NLR (d-NLR; 4.43 vs 1.5; P = 0.0002) were significantly high in SARS-CoV-2 patients. Further correlation analysis revealed a significant association of neutrophilia with the severity of the disease in SARS-CoV-2 infected patients. Moreover, receiver operating characteristic (ROC) analysis of derived CBC parameters (NLR, d-NLR, and platelet - to-lymphocyte ratio [PLR] with disease severity and disease outcome) revealed d-NLR as better predictive marker of disease severity (area under the curve [AUC] = 0.658) and disease outcome (AUC = 0.766) compared to PLR with disease severity (AUC = 0.645) and disease outcome (AUC = 0.693).

Conclusion: We therefore conclude, of the CBC parameters neutrophilia as the marker of disease severity and among derived parameters, d-NLR as an early predictive biomarker of both disease severity and poor disease outcome in SARS-CoV-2 patients.

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Introduction

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia (1). WHO declared COVID-19 a global health emergency on January 30, 2020, and characterized it pandemic on 11 March 2020 (2). As there have been 775,335,916 confirmed cases of COVID-19, including 7,045,569 deaths worldwide reported to WHO, and India recorded a total of 45,035,393 COVID-19 cases, including 533,570 deaths. (3)

In inflammation seen in viral pneumonia, such as COVID-19, an imbalance of immune response is seen as a result of severe inflammatory response and poor immune response (4). As a result, circulating biomarkers of inflammation and the immune system can serve as reliable predictors of the prognosis for COVID-19 patients (5). Of these, white blood cell (WBC) count, neutrophil (NEU) to lymphocyte (LYM) ratio (NLR), and platelet to-lymphocyte-ratio (PLR) levels help predict the prognosis of patients with viral pneumonia. The neutrophil/lymphocyte ratio (NLR) is associated with the progression of the infection and can be utilized by physicians to identify high-risk or deteriorating patients at an early stage (6). NLR includes two different leukocyte subsets, reflecting both the degree of systemic inflammation and the equilibrium of the body's neutrophil and lymphocyte counts. It more properly depicts the balance between the degree of inflammation and the state of the body's immunity (7). The dNLR was derived from the assumption that the white cell count is made up primarily of lymphocytes and neutrophils, and therefore, the white cell count minus the neutrophil count would be broadly similar to the lymphocyte count (8). The platelet-to-lymphocyte-ratio (PLR) is an integrated reflection of two important opposite inflammatory pathways easily calculated from a complete blood count. Platelet to lymphocyte ratio is also an economical tool and more predictive than either the platelet or the lymphocyte counts alone. As markers of inflammation, various studies have demonstrated the correlation between NLR, d-NLR, PLR, and many diseases such as inflammatory diseases (9), cardiovascular diseases (10), cancer (11), and COVID-19 (12).

In this study, we comparatively analyzed the CBC profile and determined the association of the various CBC parameters with severity and disease outcome in SARS-CoV-2 infected patients from Kashmir with an ultimate aim to discover CBC parameters of diagnostic and/ prognostic significance in SARS-CoV-2 infected patients from Kashmir.

Methods

The study was performed on the patients admitted in the Government Medical College Srinagar and associated SMHS Hospital from Aug 2021 to Jan 2022. The purpose of the research was explained to the participants. All participants consented (in a written form) to be involved in this research. Patients who were COVID-19-positive (confirmed by RT-PCR of the swab) were included in the study. This observational Cohort study enrolled 75 Patients (48 females, 27 males). The patients were categorized based on the severity of the disease according to WHO guidelines (13): Moderately ill: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO2) ⩾94% on room air at sea level. Severely ill: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50% and, critically ill: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction, which later failed to survive.

Inclusion criteria:

a) **Patients group:** 75 SARS-CoV-2 infected (confirmed by positive RT-PCR of the swab) patients admitted to the hospital for treating covid-19 of varying severity during the course of the study. The patients were followed until death or discharge for a maximum of 28 days.

b) **Control group:** 20 healthy individuals that were negative for SARS-CoV-2 confirmed by negative RT-PCR of the swab.

Exclusion criteria:

a) Immuno-compromised or patients with any immunological disorders.

Fully auto Sysmex-XN-1000 hematology analyzer was used for the analysis of the complete blood count.

The data was analyzed using IBM Statistical Package for the Social Sciences (SPSS) software 26. Descriptive statistics was performed and data was presented as frequency (N) and percentage (%). Continuous data was presented as mean and standard deviation. Chi-square test and student's t test were used to compare proportions between groups as deemed proper by the statistical expert. ROC analysis was carried to determine the prognostic value of CBC parameters. A P-value of less than 0.05 was considered statistically significant.

Results

In this study, a total of 75 cases that were diagnosed (confirmed positive by RT-PCR) with COVID-19 and admitted to SMHS hospital for management were taken. The Socio-demographic and clinical characteristics of the cases are shown in Table 1. Out of total 75 patients, 78.66% of the cases were >50 years and were mostly females (64%) and most of the patients were of rural origin (58.66%). Among the patients under study, cough was the major symptom present (72% of cases) followed by fever (57.33%) and pneumonia (56%). Most of the CoV-2 infected patients admitted to our hospital were with comorbidities (77.33%) including hypertension (61.33%), diabetes (29.33%), COPD (13.33%), and hypothyroidism (10.66%). Based on the severity of the infection of SARS CoV-2 the patients were divided into two groups: moderate and severe (including critical). It was found that moderate cases were more (78.66%) than severe cases (21.33%). On comparative CBC analysis of COVID-19 patients (55.33%), it was found that the majority of the patients were having low levels of Hemoglobin. Among SARS-CoV-2 infected patients 69.33% were with low percentage of lymphocytes compared to normal. It was found that a greater % of covid-19 patients (74.66%) had high levels of neutrophils. It was observed that the platelet count was normal only in 58.666% of patients.

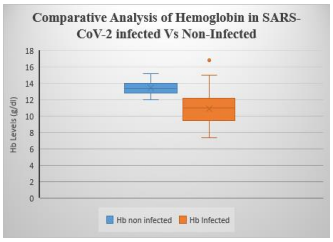
Table1. Socio-Demographic and clinical features of RT-PCR confirmed SARS-COV-2 infected patients admitted to SMHS Hospital (N=75)

Feature	Cases (n=75)	Percentage %
Age		
≤ 50	15	20
> 50	60	80
Gender		
Male	27	36
Female	48	64
Dwelling		
Rural	44	58.66
Urban	31	41.33
Severity		
Moderate	59	78.66
Severe	16	21.33
Symptoms		
Fever		
Yes	43	57.33
No	32	42.66
Cough		
Yes	54	72
No	21	28
Pneumonia		
Yes	42	56
No	33	44
Comorbidity		
Yes	58	(77.33 %)
No	17	(22.66 %)
Hypertension		
Yes	46	61.33
No	29	38.66
Diabetes		
Yes	22	29.333
No	53	70.666
COPD		
Yes	10	13.33
No	65	86.66
Hypothyroidism		
Yes	8	10.66
No	67	89.33
Vaccinated		
Yes	2	2.66
No	73	97.33
CBC profile		
Hemoglobin		
Normal	26	34.66
Low	49	55.33
TLC×10^3/µL		
Normal	57	76
High	14	18.666
Low	4	5.333
Lymphocyte (%)		
Normal	23	30.66
Low	52	69.33
Neutrophil (%)		
Normal	19	25.33
High	56	74.66
Platelet×10^3/µL		
Normal	44	58.66
Abnormal	31	41.33

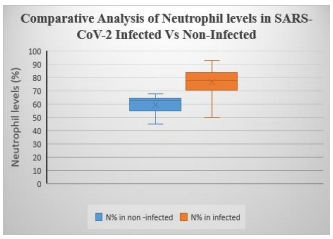
Table 2 represents comparison of CBC parameters (laboratory and derived values) of COVID-19 patients vs. non-infected. The significance of CBC parameters between COVID-19–positive and COVID-19–negative individuals was assessed by Student t test. Compared to normal individuals, mean Hemoglobin levels (13.43 Vs 10.9g/dl) (p=0.0001) (Figure 1a), Lymphocyte% (16.04 Vs 30.80) (Figure 1c), Monocyte% (5.53 Vs 7.53) (p=0.009) (Figure 1d), platelet count (150 Vs 186) (p=0.037) (Figure 1e) were significantly lower in SARS-COV-2 infected patients. Neutrophil % (76.77 Vs 59.26) (P=0.00001) was significantly higher (Figure 1b). Neutrophil-to-lymphocyte ratio (NLR) was significantly higher in covid-19 patients (7.31 Vs 2.04) (P=0.001) (Figure 1f), derived Neutrophil-to lymphocyte (dNLR) ratio was also significantly high (4.43 Vs 1.5) with p=0.0002 (Figure 1g).

Table 2. Comparative analysis of CBC profile of SARS-COV-2 infected vs non- infected (Controls)

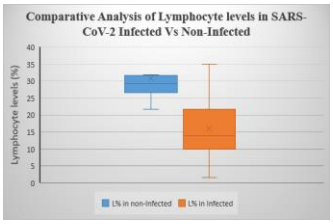
Parameters	SARS-CoV-2 infected	SARS-CoV-2 non-infected	T test	P Value
Hb (g/dl) (M ±SD)	10.959 ± 2.0266	13.438 ± .9314	- 4.361	0.00001
TLC×103/µL (M ±SD)	9.069 ± 3.91	7.273 ± 1.332	1.62895	0.05349
Neutrophil% (M ±SD)	76.77 ± 10.26	59.269 ± 7.595	5.776	0.00001
Lymphocyte% (M ±SD)	16.04 ± 8.98	30.808 ± 7.303	- 5.639	0.00001
Monocyte% (M ±SD)	5.35 ± 2.59	7.531 ± 1.832	- 2.505	0.0095
Platelet×10^3/µL (M ±SD)	150 ± 68.11	186.38 ± 59.80	- 1.806	0.037
NLR (M ±SD)	7.31 ± 5.744	2.04 ± 0.605	3.143	0.001
d-NLR (M ±SD)	4.430 ± 2.882	1.526 ± 0.423	3.585	0.0002
LMR (M ±SD)	3.76 ± 2.02	4.445 ± 1.898	- 0.901	0.187
PLR (M ±SD)	159.23 ± 164.89	86.710 ± 27.639	1.574	0.059



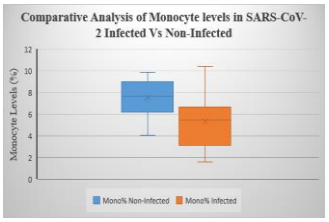
(a) (p=0.00001)



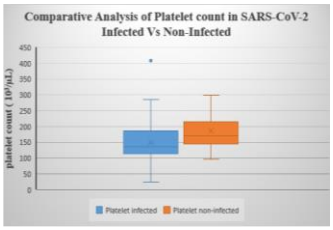
(b) p=0.00001



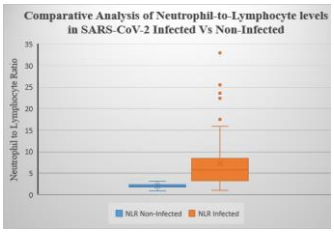
(c) p=0.00001



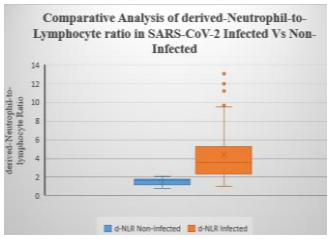
(d) p=0.0095



(e) p=0.037



(f) p=0.001



(g) p=<0.0002

Figure 1: **1a**. Box-whisker Plot representing hemoglobin levels of SARS-CoV-2 patients vs non-Infected (p=<0.001); **1b**. Box-Whisker plot representing comparative percentage of neutrophils in SARS-CoV-2 infected patients vs non- infected (p=<0.001); **1c**. Percentage of lymphocytes in SARS-CoV-2 infected vs non-infected represented by Box-Whisker Plot (p=<0.001); **1d**. Monocyte % in SARS-CoV-2 infected vs non-infected represented by Box-Whisker Plot (p=0.009); **1e**. Platelet count in SARS-CoV-2 infected vs non-infected represented by Box-Whisker Plot (p=0.037); **1f.** NLR in SARS-CoV-2 infected vs non-infected represented by Box-Whisker Plot (p=0.001); **1g**. d-NLR in SARS-CoV-2 infected vs non-infected represented by Box-Whisker Plot (p=<0.001)

Table 3 represents association of socio-demographic features and clinical characteristics of SARS-CoV-2 Infected patients with the severity of disease. Significant association was found between high neutrophil percentage and the

severity of the disease (p=0.047). Though not statistically significant an association was found between lymphopenia and severity of the COVID-19.

Table 3. Association of various socio-demographic features and CBC parameters of SARS-CoV-2 patients with the severity of disease

Parameters	Cases (n=75)	Severity		χ2	P value
		Moderate 59 (78.66%)	Severe 16 (21.33%)		
Age					
≤ 50	15 (21.33%)	13	2	0.715	0.397
>50	60 (78.66%)	46	14		
Gender					
Male	27 (36%)	21	6	0.019	0.887
Female	48 (64%)	38	10		
Dwelling					
Rural	44 (58.6%)	35	9	0.049	0.824
Urban	31 (41.33%)	24	7		
Fever					
Yes	43 (57.33%)	32	11	1.083	0.297
No	32 (42.66%)	27	5		
Cough					
Yes	54 (72%)	42	12	0.090	0.763
No	21 (28%)	17	4		
Pneumonia					
Yes	42 (56%)	30	12	2.979	0.084
No	33 (44%)	29	4		
Comorbidities					
Yes	58 (77.33%)	48	10	2.553	0.110
No	17 (22.66%)	11	6		
CBC profile					
Hemoglobin					
Normal	26	22	4	0.839	0.359
Low	49	37	12		
TLC×10^3/µL					
Normal	57 (76%)	45	12	0.011	0.915
Abnormal	18 (24%)	14	4		
Neutrophilia					
Yes	56 (74.66%)	41	15	3.915	0.047
No	19 (25.33%)	18	1		
Lymphopenia					
Yes	52 (69.33%)	38	14	3.157	0.075
No	23 (30.66%)	21	2		
Platelet×10^3/µL					
Normal	44 (58.66%)	36	7	0.872	0.350
Abnormal	31 (41.33%)	23	8		

No defined laboratory reference values were found for NLR, d-NLR, PLR in SARS-CoV 2 infected patients. In order to find the association of NLR, d-NLR, PLR with severity of disease, we analyzed the optimal cut-off values for each of these parameters calculated by the ROC analysis, and the ROC curves were presented in Figure 2. The areas under the curve (AUC) of NLR, d-NLR, and PLR were 0.631, 0.658, and 0.645 respectively (Table 4). Though each of these parameters revealed an association with the severity of the disease, however, AUC of d-NLR was found statistically significant (p=0.05). The optimal cut-off value for d-NLR was 3.45 with sensitivity (68%) and specificity (50%).

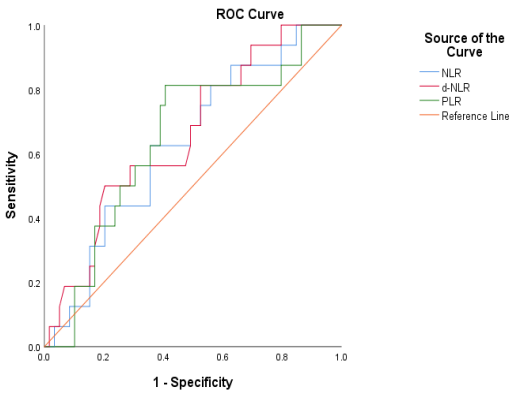


Figure 2. ROC Curves for NLR, d-NLR and PLR with varied severity

Table 4. Areas under curve (AUC) for NLR, d-NLR, and PLR for severity

Test result variable (s)	Area	Std. Error [a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower bound	Upper bound
NLR	0.631	0.074	0.10	0.487	0.775
d-NLR	0.658	0.073	0.05	0.515	0.801
PLR	0.645	0.076	0.07	0.496	0.794

The ROC curves, using COVID-19 Specific death as an end-point for NLR, dNLR and PLR is shown in Figure 3. The areas under the curve (AUC) of d-NLR, NLR, and PLR were 0.766, 0.705, and 0.693 respectively (Table 5). Out of these, only d-NLR was found statistically significant (p=0.03). The optimal cut-off value of d-NLR for predicting disease outcome was 5.1. The highest sensitivity and specificity were 83% and 78% respectively.

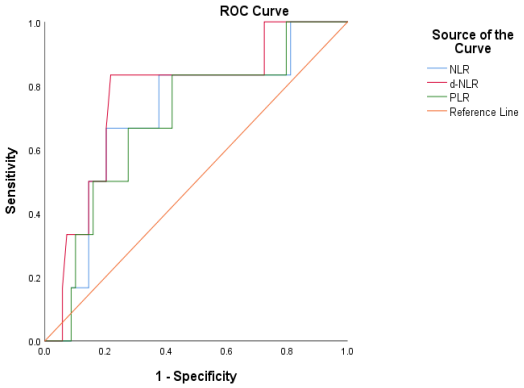


Figure 3. ROC Curves for NLR, d-NLR and PLR with disease outcome

Table 5. Areas under curve (AUC) for d-NLR, NLR, and PLR for disease outcome

Test result variable (s)	Area	Std. Error [a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower bound	Upper bound
NLR	0.766	0.099	0.032	0.572	0.960
d-NLR	0.705	0.108	0.097	0.493	0.917
PLR	0.693	0.108	0.118	0.482	0.904

Discussion

Severe acute respiratory syndrome coronavirus (SARS-COV-2), known as COVID-19, is the new type of coronavirus responsible for the latest pandemic in the world (14). There are different clinical characteristics and laboratory findings that has been associated with severity, hospitalization, and mortality in COVID-19 (15). Among the baseline investigations, CBC analysis has an important role in the monitoring and management of COVID-19. Therefore, the present study aimed to comparatively analyze CBC parameters (normal and derived) in SARS-CoV-2 infected patients and normal non- infected subjects admitted to SMHS hospital from Kashmir. In the present study hemoglobin, neutrophils, lymphocytes, monocytes were found the most common deranged CBC parameters in SARS-CoV-2 infected patients. Analysis of derived CBC parameters revealed dNLR as an early predictive marker of disease severity and poor disease outcome in SARS-CoV-2 patients from Kashmir. On CBC analyses of peripheral blood, Hemoglobin was found significantly low in COVID-19 patients. The possible mechanism of low Hb in SARS-CoV-2 infected patients could be the inflammation that can alter iron hemostasis and reduce intestinal iron absorption, resulting in the reduced availability of the metal for erythropoiesis and the production of hemoglobin (Hb) (16). In our study Neutrophil count was found significantly high among the SARS-CoV-2 Infected patients compared to normal (p=0.0001). Neutrophil is a major component of the leukocyte population that activates and migrates from the venous system to the immune organ or system upon infection. Moreover, neutrophil can also be activated by virus-related inflammatory factors, such as IL-6 and IL-8, TNF-α and G-CSF, and INF-γ factors, produced by lymphocyte and endothelial cells (17-20). Neutrophils are known to release large amounts of ROS that can induce cell damage and free the virus from the cells. The antibody dependent cell mediated cell (ADCC) may kill the virus directly or expose virus antigen and stimulate cell-specific and humoral immune response (21). In addition, neutrophils are reported to increase the expression of 45 circulating vascular endothelial growth factor (VEGF) in COVID-19 patients (22) that markedly contributes to tissue and organ damage. This fact was substantiated here also as the significant association was found between high neutrophil percentage and the severity of disease (Table 4). Lymphopenia is a common feature in COVID-19 so was found in this study. Lymphocytes play a conclusive role in upholding immune homeostasis and inflammatory response throughout the body. On comparative analysis, lymphocytes were significantly low in SARS-CoV-2 infected patients (p=0.0001). There are four possible potential mechanisms that can lead to lymphocyte deficiency in SARS-CoV-2 infected patients. (i) The SARS-CoV-2 virus might directly infect lymphocytes as they bear ACE2 receptors which are its common targets (23). (ii) The SARS-CoV-2 virus might directly destroy lymphatic organs such as thymus and spleen decreasing the production of lymphocytes. (iii) Inflammatory cytokines like tumor necrosis factor (TNF)α, interleukin (IL)-6, have been found deranged in SARS-CoV-2 infected patients perhaps leading to lymphocyte apoptosis (24). (iv) Inhibition of lymphocytes by metabolic molecules produced by metabolic disorders, such as hyperlactic acidemia as reported in the severe type of COVID-19 patients (25).

Decreased monocyte cells are also a characteristic feature of COVID-19 so was observed in our study. On comparative analysis the monocytosis was found significantly low among SARS-CoV-2 infected patients (p=0.009). Acute and chronic inflammation results in systemic monocytosis so is observed in SARS infected patients. Monocytes are recruited to inflammatory sites where they mediate inflammation and differentiate into tissue macrophages. Blood monocytosis enables eradication of infection and removal of cellular debris after injury and ischemia. Monocyte-derived macrophages may also support resolution of inflammation, if their phenotype permits. However, exaggerated monocytosis during inflammation likely harms tissues by limiting resolution of inflammation and propagating exaggerated immune activation (26). On comparative analysis significantly low levels of platelet count was found in SARS infected patients compared to normal individual (p=0.03). So reduced platelet count is characteristic CBC feature associated with COVID-19 infection. The low platelet count, generally observed in viral infections can lead to thrombocytopenia in SARS-CoV-2 infected patients too. The possible reason for low platelet count is the activation of platelets either by viral antigen antibody complexes or host inflammatory responses leading to clearance of activated platelets by the reticuloendothelial system (27). Viruses can also interact with megakaryocytes and reduce platelet synthesis so must be true for SARS-CoV-2. (28). After the discussion of the basic parameters of Complete Blood Count of COVID-19, we analyzed the different ratios of CBC parameters which include NLR, PLR, d-NLR in patients with COVID-19. From the AUC analysis of NLR, dNLR and PLR, d-NLR was found as an early prognostic biomarker of disease severity in SARS-CoV-2 infected patients. The applicable thresholds for NLR, d-NLR, PLR, were observed using the ROC curve. The optimal threshold at 3.45 for d-NLR showed a superior prognostic risk of clinical symptoms to change from mild to severe, which had the highest of sensitivity (68%) and specificity (50%) and the largest of AUC i.e., 0.658. So, these patients require diligent attention by clinician. On ROC curve analysis of derived parameters d-NLR was the only significant parameter to predict poor disease outcome with AUC= 0.766 having highest specificity (78%) and sensitivity (83%).

Conclusion

From this study, we concluded among CBC parameters increased neutrophilia as significantly associated with the severity of disease. Among the derived CBC parameters, d- NLR, turns out to be a predictive biomarker for severity of the disease (AUC=0.658, at specificity of 50% and sensitivity of 68%) as well as for poor disease outcome (AUC=0.766, at specificity of 78% and sensitivity of 83%).

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Ethical statement

The work was ethically approved by the ethical committee of GOVT Medical College and associated SMHS Hospital. Approval no: Ref No.IEC-GMC-Sgr/27.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Authors IJ and RE have contributed to the design and implementation of the study. Authors IJ and IF have carried out the data collection of the work. Authors IJ and IF did the formal analysis. Author SF investigated the work. Authors IJ, SS, RE, and SM wrote the original draft as well as edited the manuscript. The final manuscript was read and approved by all authors.

References

1. WHO. Novel coronavirus - China. 2020. [View at Publisher] [Google Scholar]
2. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020. [View at Publisher]
3. WHO. WHO COVID-19 dashboard: COVID-19 cases. 2023. [View at Publisher]
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33. [View at Publisher] [DOI] [PMID] [Google Scholar]
5. Xiang N, Havers F, Chen T, Song Y, Tu W, Li L, et al. Use of national pneumonia surveillance to describe influenza A (H7N9) virüs epidemiology, China, 2004-2013. Emerg Infect Dis. 2013;19(11):1784-90. [View at Publisher] [DOI] [PMID] [Google Scholar]
6. Feng X, Li S, Sun Q, Zhu J, Chen B, Xiong M, et al. Immune-Inflammatory Parameters in COVID-19 Cases: A Systematic Review and Meta-Analysis. Front Med. 2020;7:301. [View at Publisher] [DOI] [PMID] [Google Scholar]
7. Soylu K, Gedikli Ö, Ekşi A, Avcıoğlu Y, İdil Soylu A, Yüksel S et al. Neutrophil-to-lymphocyte ratio for the assessment of hospital mortality in patients with acute pulmonary embolism. Arch Med Sci. 2016;12(1):95-100. [View at Publisher] [DOI] [PMID] [Google Scholar]
8. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer. 2012;107:695-9. [View at Publisher] [DOI] [PMID] [Google Scholar]
9. Alan S, Tuna S, Türkoğlu EB. The relation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume with the presence and severity of Behçet's syndrome. Kaohsiung J Med Sci. 2015;31(12):626-31. [View at Publisher] [DOI] [PMID] [Google Scholar]
10. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. Atherosclerosis. 2014;234(1):206-13. [View at Publisher] [DOI] [PMID] [Google Scholar]
11. Bowen RC, Little NAB, Harmer JR, Ma J, Mirabelli LG, Roller KD, et al. Neutrophil-to-lymphocyte ratio as prognostic indicator in gastrointestinal cancers: a systematic review and meta-analysis. Oncotarget. 2017;8(19):32171-89 [View at Publisher] [DOI] [PMID] [Google Scholar]
12. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504. [View at Publisher] [DOI] [PMID] [Google Scholar]
13. National Institutes of Health. COVID-19 Treatment Guidelines Panel; Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2022. [View at Publisher]
14. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: epidemiological, clinical and immunological features and hypotheses. Cell Stress. 2020;4(4):66-75. [View at Publisher] [DOI] [PMID] [Google Scholar]
15. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, et al. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 infection in Lombardy, Italy. J Clin Med. 2020;9(5):1548. [View at Publisher] [DOI] [PMID] [Google Scholar]
16. Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, et al. Prevalence and predictive value of Anemia and Dysregulated Iron homeostasis in patients with COVID-19 infection. J Clin Med. 2020;9(8):2429. [View at Publisher] [DOI] [PMID] [Google Scholar]
17. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Intern Med. 2000;248(3):171-183. [View at Publisher] [DOI] [PMID] [Google Scholar]
18. Blaser MJ, Chyou PH, Nomura A. Age at Establishment of Helicobacter pylori Infection and Gastric Carcinoma, Gastric Ulcer, and Duodenal Ulcer Risk. Cancer Res. 1995;55(3):562-5. [View at Publisher] [PMID] [Google Scholar]
19. Scholl SM, Pallud C, Beuvon F, Hacene K, Stanley ER, Rohrschneider L, et al. Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. J NatI Cancer Inst. 1994;86(2):120-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
20. Shacter E, Weitzman SA. Chronic inflammation and cancer. Oncology (Williston Park). 2002;16(2):217-26. [View at Publisher] [PMID] [Google Scholar]
21. Kusumanto YH, Dam WA, Hospers GAP, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis. 2003;6(4):283-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
22. Kim SL, Lee ST, Trang KTT, Kim SH, Kim IH, Lee SO. Parthenolide exerts inhibitory effects on angiogenesis through the downregulation of VEGF/VEGFRs in colorectal cancer. Int J Mol Med. 2014;33(5):1261-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
23. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8. [View at Publisher] [DOI] [PMID] [Google Scholar]
24. Liao YC, Liang WG, Chen FW, Hsu JH, Yang JJ, Chang MS. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol. 2002;169(8):4288-97. [View at Publisher] [DOI] [PMID] [Google Scholar]
25. Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood. 2007;109(9):3812-19. [View at Publisher] [DOI] [PMID] [Google Scholar]

26. Dutta P, Nahrendorf M. Regulation and consequences of monocytosis. Immunol Rev. 2014;262(1):167-78. [View at Publisher] [DOI] [PMID] [Google Scholar]
27. Assinger A. Platelets and infection - an emerging role of platelets in viral infection. Front Immunol. 2014;5:649. [View at Publisher] [DOI] [PMID] [Google Scholar]
28. Seyoum M, Enawgaw B, Melku M. Human blood platelets and viruses: defense mechanism and role in the removal of viral pathogens. Thromb J. 2018;16(1):16. [View at Publisher] [DOI] [PMID] [Google Scholar]

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