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Associations between complete blood count-derived inflammatory indices and COVID-19 severity: A retrospective case-control study

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ABSTRACT

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is the causative organism of coronavirus disease (COVID)-19 disease. It is associated with systemic inflammatory response characterized by multiorgan involvement. Depending on the extent of involvement of the lungs, the infection can be categorized as mild, moderate, and severe. This retrospective case-control study aimed to assess the severity of COVID-19 infection using hematological parameters like total and differential white blood cell, platelet, and certain derived indices like neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), platelet lymphocyte ratio (PLR), systemic inflammatory index (SII), and systemic inflammatory response index (SIRI). The study was carried out at the tertiary care teaching hospital in Chennai, India. The study included 455 COVID-19 patients who underwent treatment in the year 2020 (pre-vaccination period), aged more than 18 years, confirmed by reverse transcriptase PCR of nasopharyngeal swabs for SARS-CoV-2. There were mild (n=320), moderate (n=70), and severe (n=65) COVID-19 cases. Around 270 patients who attended the Department of General Medicine for ailments other than COVID-19 and who were negative for COVID-19 testing were treated as controls. NLR, SII and SIRI were noticeably elevated and were associated with severe form of the disease, reflecting heightened immune activation and dysregulation. Hematological abnormalities of white blood cells and platelets, highlight the impact of cytokine-mediated inflammation. SIRI and SII showed good receiver operating characteristics curve performances. SIRI was associated with other inflammatory variables better than SII. Thus, NLR, SII, and SIRI may serve as reliable, and cost-effective laboratory tests for assessing the severity of COVID-19 infection.

Keywords: *COVID-19; inflammation; complete blood count and hematological ratios*

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan, China. The clinical features of COVID-19 are fever, myalgia, sore throat, loss of smell and taste, headache, diarrhea, weakness, cough, running nose and difficulty in breathing in severe cases (Agarwal et al., 2020; Lv et al., 2020). It poses a major challenge to clinicians in terms of early risk stratification and management (Karimi et al., 2021). The inflammation is due to interaction of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) receptors. The virus targets type II pneumocytes in the lungs, and also the epithelial cells of the proximal convoluted tubule of kidney. Viral infection causes a reduction in ACE2 levels, disrupting the regulation of angiotensin II and the renin-angiotensin system (RAS) in lungs, heart, blood vessels, and kidneys. This facilitates progression of COVID-19 from mild or moderate illness to a more severe form. Direct infection of endothelial cells leads to widespread activation of coagulation pathways, platelet aggregation, and stimulation of monocytes and neutrophils in the target organs. These findings highlight the central role of ACE2 in the pathogenesis of COVID-19 (Oudit et al., 2023).

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Patients with severe COVID-19 present with microvascular complications with prolonged prothrombin time, elevated D-dimer, ferritin etc. (Munjal et al., 2020). The gold standard method for the diagnosis of COVID-19 is real-time reverse transcriptase polymerase chain reaction (RT-PCR) along with computerized tomography (CT) of the lung to rule out the lobar involvement of the lungs, however, it does not provide information about the systemic involvement of the disease (Tria et al., 2025). Inflammatory markers—specifically the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and systemic immune response index (SIRI)—have emerged as potential diagnostic tools in COVID-19 infection. However, substantial gaps exist regarding their clinical utility in Indian COVID-19 patients, representing a critical limitation for clinical practice in the Indian healthcare system.

The most significant gap is the absence of adequately powered, multi-center prospective studies in Indian populations. While global COVID-19 research has documented these markers extensively, Indian-specific evidence remains sparse. The only published South Indian study on SII and PNI included just 80 COVID-19 patients from a single tertiary center in Bengaluru (Reddy et al., 2024). Another study from Western India examined 272 patients but focused predominantly on interleukin-6 (IL-6) rather than these inflammatory ratios (Indranil et al., 2024). The largest Indian study specifically examined NLR and PLR but was limited to a single institution (Patil et al., 2023). This study aimed to evaluate the association between NLR, MLR, PLR, SII and SIRI and COVID-19 severity, and to determine optimal cut-off values and odds ratios for these indices in predicting severe disease.

MATERIALS AND METHODS

Study design

The retrospective case-study was carried out at Sri Ramachandra Institute of Higher Education and Research, Chennai, India.

Study population

The study population included patients with COVID-19 who underwent treatment between January 2020 to December 2020 (pre-vaccination period).

Inclusion criteria: Individuals aged ≥18 years, both genders, first admission, diagnosis confirmed according to the World Health Organization (WHO) and Centre for Disease Control and Prevention (CDC) guidelines for the detection and diagnosis of COVID-19, by reverse transcriptase PCR of nasopharyngeal swabs for SARS-CoV-2. Around 455 patients with positive COVID-19 infection were recruited as cases (Moorthy et al., 2022) and availability of data of complete blood count.

The participants were classified into three groups based on the oxygen saturation in room air, including mild (n=320), moderate (n=70), and severe (n=65) cases characterized by an oxygen saturation of ≥94%, 91%– 93%, and >90%, respectively.

Exclusion criteria: Individuals less than 18 years, data of complete blood count being incomplete, hematological malignancies, immunosuppressive therapy, pregnancy, chronic inflammatory diseases.

Controls: 270 individuals who tested negative for COVID-19 infection by RTPCR. These individuals gave history of exposure to individuals with COVID-19 infection.

Data collection

The patient details regarding demographics and complete blood count were collected from the Medical Records Department of the hospital. The various indices were calculated by using the following formulae: NLR= absolute neutrophil count (ANC)/ absolute lymphocyte count (ALC), MLR = absolute monocyte count (AMC)/ ALC; PLR = platelet count (PC)/ALC; SII = (ANC × PC)/ALC; SIRI = (ANC × AMC)/ALC) (Citu et al., 2022).

Ethics statement

All the procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional ethics committee approval was obtained (IEC-NI/20/AUG/75/49, dated 08-08-2020). Waiver of informed consent, as permitted by the national regulatory body was obtained as the patients were treated and discharged from the hospital.

Statistical analysis

Statistical analysis was performed using SPSS software version 16.0. Continuous variables were expressed as median and interquartile range (IQR) and were compared by Kruskal-Wallis test with Dunn's post-hoc test. Categorical variables were expressed as frequency and percentage and were compared by Chi-square test. The Spearman correlation

coefficient was obtained. Receiver Operating Characteristic (ROC) curve was done to calculate area under the curve (AUC) and cut-off values of variables were decided based on the Youden's index. AUC values and its interpretation: ≥ 0.9: excellent, 0.8 - 0.89: considerable, 0.7 -0.79: fair, 0.6 – 0.69: poor, 0.5 -0.59: fail (Çorbacıoğlu, & Aksel, 2023). Odds ratio was calculated, to find out which variable could indicate the risk of bad prognosis or outcomes. P-value ≤ 0.05 was considered statistically significant.

RESULTS

The retrospective case-control study was done in mild (n=320), moderate (n=70), and severe (n=65) COVID-19 cases and 270 control individuals. In the present study there were 438 (60.4%) males and 287 (39.6%) females. The demographic details of the patients are shown in Table 1.

The total white blood cell (WBC) count showed a gradual increase in the median levels from mild disease to severe disease, which was statistically significant (p=0.023). The absolute neutrophil count showed gradual increase from mild to moderate, and severe cases (p=0.034). The platelet counts were statistically significantly lower in all the case groups compared to the controls, (p <0.001). The median levels of ALC decreased from controls, mild to moderate and severe cases(p=0.011). Median NLR increased progressively from controls to mild, moderate and severe cases (2.4, 1.9, 3.9 and 5.3, respectively; p<0.001), with the most pronounced rise occurring from mild to moderate/severe disease. The median PLR values showed a gradual increase from controls to cases-mild through moderate and severe cases (125.1, 133.5, 182.9, 234.0; p<0.001). SII and SIRI showed an initial decrease in mild cases compared to controls, then the levels progressively increased, resulting in a statistically significant increase in moderate and severe cases with p-values of 0.015 and 0.009 respectively (Table 1).

Table 2 shows the Spearman correlation coefficient among the variables in the study participants. The correlation coefficient 'ρ' was graded as follows: <0.09: negligible correlation, 0.10-0.39: weak correlation, 0.40-0.69: moderate correlation, 0.70-0.89: strong correlation, 0.90-1.00: very strong correlation (Hinkle et al., 2003). Table 3 and Figure 1. show the receiver operating characteristics (ROC) curve and cut-off values of the variables. Table 4 shows the odds ratio of the variables with the risk interpretation.

Correlation analysis showed very strong correlation: positive with SII, SIRI and NLR; strong correlation: Positive with SII and SIRI; moderate correlation: Positive with NLR and PLR/SII, PLR and SIRI, MLR and SIRI, and negative ALC and NLR; weak correlation: positive age and PLR, MLR with PLR and SII, PLR and SII, negative: ALC and MLR/SIRI, platelets and NLR/SIRI. Thus, inflammatory indices (NLR, SII, SIRI) were strongly intercorrelated and correlated positively with neutrophil count and total leukocyte count, but negatively with ALC (Table 2).

ROC curve was done involving cases. Mild and Moderate cases were treated as one group, while the other group consisted only of severe cases. This grouping was done since the study aimed to assess the biomarker that can identify the severity of the disease. NLR, MLR, PLR, SII and SIRI were subjected to ROC analysis. Since age could influence the variables, two models were used. Model 1 showed ROC curves of variables unadjusted for age; while model 2 consisted of variables adjusted for age. AUC curve showed better response with higher cut-off values in Model 2. Model 2 showed higher cut-off values than Model 1 (Table 3).

All the variables except MLR, showed statistical significance in both models. Model 2 showed lower odds ratio compared to Model 1. NLR showed highest OR followed by SII and PLR. Model 2 showed a narrower 95% CI compared to Model 1 (Table 4).

DISCUSSION

COVID-19 elicits the immune and inflammatory responses and causes structural and functional abnormalities of neutrophils, lymphocytes, and monocytes, as well as dysfunction in cytokine synthesis resulting in cytokine storm syndrome (Yang et al., 2020). Appropriate diagnosis and prognosis are the cornerstone for lowering disease severity and, consequently, death. After two to three weeks of the onset of the infection, the clinical appearance might vary from asymptomatic to the critical stage. The pathophysiology of COVID-19 can be classified as mild, moderate, and severe, based on the degree of lung involvement and the inflammatory process (Yang et al., 2020). Cytokine storm results from the responses of cytokines and chemokines on immune cells, leading to stimulation of activation of inflammatory reactions (Gong et al., 2020).

The retrospective case-control study was done in 455 COVID-19 cases and 270 control individuals. Around 60% were males, probably due to the presence of coexisting metabolic conditions, which are common among males. This was in alignment with the study by Adapa et al, that males were affected 1.72 times more than females (Adapa et al., 2022). The presence of comorbidities may weaken the immune functions, thus predisposing these individuals to COVID-19 infection (Guan et al., 2020). However, in the present study, the gender distribution did not show a statistically significant difference across the groups. The median age of controls and cases did not show statistical significance. When the cases were categorized into mild, moderate, and severe, statistical significance was obtained (p<0.001) (Table 1). According to Zhou et al., individuals infected with SARS-CoV-2 and older than 50 years of age are at increased risk of long hospital stays with increased morbidity and mortality (Zhou et al., 2020). The severity of COVID-19 increases with

Table 1

Demographic details and biomarkers levels of the study participants

Variable	Control (n=270)	COVID-19 Cases (n=455)			p-value
		Mild (n=320)	Moderate (n=70)	Severe (n=65)	
Age (year)	57 (49-65)	50 (37-58) [a]	56.5 (48-63) [b]	60.5 (54-68) [a,b]	<0.001**
Gender n (%) #					
Male	164 (60.7)	185 (57.8)	45 (64.0)	44 (67.6)	0.42
Female	106 (39.3)	135 (42.2)	25 (36.0)	21 (33.4)	
Hb (g/dL)	12.7 (11.3-14.3)	12.9 (11.9-14.1)	12.4 (11.4-13.7)	12.7 (11.05-13.7)	0.07
TC (cells/c.mm)	8535 (7100-10170)	5900 (4800-7300) [a]	6700 (5100- 8700) [a,b]	7200 (5600-10000) [a,b]	0.023*
ANC (cells/c.mm)	5503 (4270-6912)	3464 (2580-4626) [a]	4488 (3440-6807) [a,b]	5984 (4071-8326) [b,c]	0.034*
ALC (cells/c.mm)	2105 (1550-2822)	1720 (1357-2221) [a]	1116 (801-1744) [a,b]	999 (704-1344) [a,b]	0.011*
AMC (cells/c.mm)	479 (314-648)	549 (413-673) [a]	473 (373-628) [b]	535 (364-739)	0.002**
Platelet (x10^5 cells /c.mm)	2.7 (2.1-3.4)	2.3 (1.9-2.8) [a]	2.2 (1.8-2.6) [a]	2.3 (1.7-2.9) [a]	<0.001**
NLR	2.4 (1.7-3.8)	1.9 (1.3-2.8) [a]	3.9 (2.5-6.8) [a,b]	5.3 (3.1-13.1) [a,b]	0.001**
MLR	0.2 (0.1– 0.3)	0.3 (0.2-0.4) [a]	0.3 (0.3-0.5) [a,b]	0.4 (0.3-0.7) [a,b]	0.03*
PLR	125.1 (85.2-180.1)	133.5 (100.8-174.5)	182.9 (126.7-313.6) [a,b]	234.0 (128.4-367.6) [a,b]	<0.001**
SII	640.2 (411.5-1184.4)	450.7 (280.3-704.9) [a]	883.1 (467.5-1734.1) [b]	1216.1 (610.4-3768.4) [a,b]	0.015*
SIRI	1136.8 (634.1-1997.4)	996.0 (635.6-1719.1)	1798.8 (1132.9-2948.9) [a,b]	2879.0 (1348.0-6810.3) [a,b,c]	0.009**

*Note: TC: total white blood cell count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, AMC: absolute monocyte count, NLR: neutrophil lymphocyte ratio, MLR: monocyte lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: systemic immune inflammation index, SIRI: systemic inflammatory response index. Variables were expressed in median and interquartile range (Kruskal-Wallis test with Dunn's post-hoc test used). [#]: expressed as frequency and percentage (Chi-square test used) *: significant p-value, **: highly significant p-value. Intergroup comparison (Dunn's test): [a]: control vs mild/ moderate/ severe; [b]: mild vs moderate/ severe; [c]: moderate vs severe.*

Table 2

Spearman correlation of the biomarkers among the study participants.

Variable	Age	Hb	TC	ANC	ALC	AMC	Platelets	NLR	MLR	PLR	SII	SIRI
Hb	-0.127 <0.001	—										
TC	0.089 0.04	0.067 0.53	—									
ANC	0.052 0.67	0.082 0.03	0.847 <0.001	—								
ALC	-0.198 <0.001	0.156 <0.001	0.181 <0.001	0.060 0.25	—							
AMC	0.134 <0.001	-0.023 0.62	0.234 <0.001	0.189 <0.001	0.089 0.04	—						
Platelets	-0.091 0.04	0.252 <0.001	-0.090 0.05	-0.123 <0.001	0.275 <0.001	-0.067 0.58	—					
NLR	0.156 <0.001	-0.089 0.04	0.456 <0.001	0.523 <0.001	-0.567 <0.001	0.189 <0.001	-0.234 <0.001	—				
MLR	0.092 0.04	-0.156 <0.001	0.256 <0.001	0.267 <0.001	-0.247 <0.001	0.467 <0.001	-0.189 <0.001	0.244 <0.001	—			
PLR	0.282 <0.001	-0.198 <0.001	0.189 <0.001	0.258 <0.001	-0.456 <0.001	0.123 <0.001	0.512 <0.001	0.567 <0.001	0.189 <0.001	—		
SII	0.123 <0.001	-0.067 0.98	0.764 <0.001	0.912 <0.001	-0.189 <0.001	0.252 <0.001	-0.156 <0.001	0.687 <0.001	0.298 <0.001	0.345 <0.001	—	
SIRI	0.187 <0.001	-0.123 <0.001	0.732 <0.001	0.798 <0.001	-0.267 <0.001	0.298 <0.001	-0.215 <0.001	0.923 <0.001	0.634 <0.001	0.456 <0.001	0.845 <0.001	—

Note: Strong positive (≥0.5); Moderate positive (0.3–0.49); Weak positive (0.1–0.29); Neutral (~0): Strong negative (≤−0.5); Moderate negative (−0.3 to −0.49); Weak negative (−0.1 to −0.29). Hb: Hemoglobin, TC: Total WBC count, ANC: Absolute Neutrophil Count, ALC: Absolute Lymphocyte Count, AMC: Absolute Monocyte Count, PLT: Platelet count, NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index. Shown are rho and p-values.

Table 3

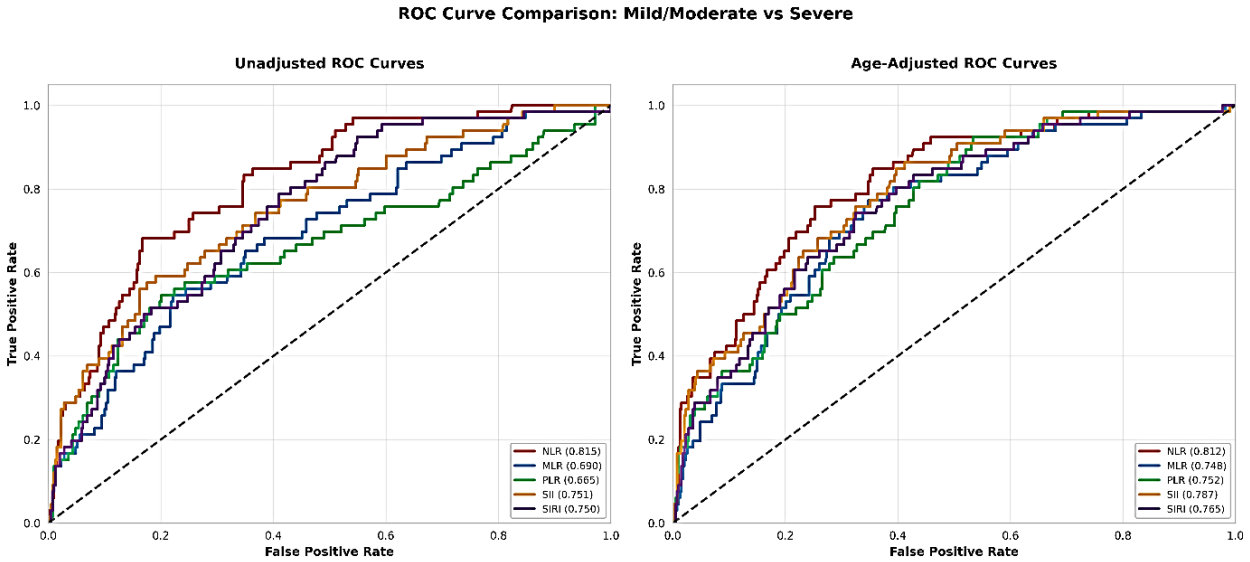
Receiver Operating Characteristics (ROC) of the variables.

Biomarker	Model	AUC (95% CI)	p-value	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	1	0.815 (0.762-0.863)	<0.001**	4.47	68.18	83.25	40.90	93.89
MLR	1	0.690 (0.616-0.757)	<0.001**	0.48	54.55	77.84	29.50	90.96
PLR	1	0.665 (0.579-0.745)	<0.001**	220.88	54.55	79.91	31.57	91.17
SII	1	0.751 (0.685-0.814)	<0.001**	1096.05	57.58	82.47	35.58	91.95
SIRI	1	0.750 (0.686-0.808)	<0.001**	21.80	78.79	59.02	24.64	94.23
NLR	2	0.812 (0.758-0.865)	<0.001**	17.92	75.76	74.74	73.68	88.04
MLR	2	0.748 (0.684-0.809)	<0.001**	2.72	77.27	65.21	51.23	85.94
PLR	2	0.752 (0.694-0.810)	<0.001**	928.29	92.42	46.65	73.23	86.71
SII	2	0.787 (0.731-0.842)	<0.001**	5996.18	84.85	60.31	68.42	87.81
SIRI	2	0.765 (0.704-0.824)	<0.001**	152.94	74.24	67.53	54.54	86.45

Note: ROC: Receiver Operating Characteristic, AUC: Area Under Curve, NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index, PPV: Positive Predictive Value, NPV: Negative Predictive Value, CI: Confidence Interval. Diagnostic performance of hematological indices (NLR, MLR, PLR, SII, SIRI) in predicting severe COVID-19. Two models were analyzed: Model 1 - ROC analysis unadjusted for age, Model 2 - ROC analysis adjusted for age. Cut-off values were determined using Youden's index. Sensitivity, specificity, PPV, and NPV are provided to show predictive accuracy. NLR consistently showed the highest AUC and odds ratio, making it the most reliable biomarker for severity prediction.

Figure 1

Receiver Operating Characteristics (ROC) of selected variables.



Note: NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index. ROC curves illustrate diagnostic performance of NLR, MLR, PLR, SII, and SIRI. Two models are shown: Model 1 - Unadjusted for age, Model 2 - Adjusted for age.

Table 4

Odds ratio for Severe Disease based on age-adjusted cut-off mild/moderate vs severe cases.

Biomarker	High Risk (n)	Low Risk (n)	Model 1- OR (95% CI)	p-value	Model 2- OR (95% CI)	p-value
NLR	19	435	20.62 (7.13 - 59.61)	<0.001**	13.08 (4.41 - 38.74)	<0.001**
MLR	6	448	6.11 (1.21 - 30.95)	0.057	2.13 (0.39 - 11.52)	0.381
PLR	10	444	15.23 (3.83 - 60.52)	<0.001**	8.59 (2.05 - 36.00)	0.003**
SII	19	435	15.62 (5.69 - 42.84)	0.002**	9.88 (3.50 - 27.93)	<0.001**
SIRI	11	443	7.66 (2.27 -25.88)	0.003**	3.76 (1.06 - 13.39)	0.041*

Note: OR: Odds Ratio, CI: Confidence Interval, NLR: Neutrophil-to-Lymphocyte Ratio, MLR: Monocyte-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, SIRI: Systemic Inflammatory Response Index. Odds ratios (OR) with 95% confidence intervals (CI) for each biomarker in predicting severe COVID-19. Two models were analyzed: Model 1 - Unadjusted values, Model 2 - Age-adjusted values. NLR showed the highest OR, followed by SII and PLR, indicating their strong predictive value for severe disease. p value ≤ 0.05 was considered statistically significant.

age, and hospital stay is longer in older compared to younger age (Kalantari et al., 2020). The total WBC count showed a gradual increase in the median levels from mild to severe disease, which was statistically significant (p=0.023). The ANC showed 5503, 3464, 4488, and 5984 in control, mild, moderate, and severe cases, respectively (p=0.034). Among the cases, there were statistically significant differences showing that there was a gradual increase in ANC as the severity of the disease increased. The median levels of ALC count were decreased in all three case groups compared to those of controls (p=0.011). AMC in the mild and severe cases was higher than that of the controls. They dropped to the levels of the controls in moderate cases. This probably could be due to the varied response of the cytokines and other inflammatory mediators in the initial stages, as well as with the advancement of the disease (Table 1).

According to Al-Saadi and Abdulnabi (2021), lymphocytopenia is due to cytokine storm and lysis of lymphocytes by the COVID-19 virus, as lymphocytes also express angiotensin converting enzyme (ACE)2 in tissues (Al-Saadi & Abdulnabi, 2021). Haematological alterations in non-severe cases are mild and primarily consist of lymphocytopenia. Neutrophilia, lymphocytopenia, increased D-dimer, prolonged prothrombin time (PT), and decreased

fibrinogen are indicators of disease progression and unfavourable outcome in patients with severe disease (Al-Saadi & Abdulnabi, 2021). Lymphopenia is also associated with thrombocytopenia in a few cases. Viral infections can cause neutropenia. Neutropenia is characterized by a decrease in ANC to less than 1500 cells/mL. It is due to either bone marrow suppression or peripheral destruction of neutrophils (Esmaeili & Esmaeili, 2025).

Inflammatory markers such as NLR, MLR, and PLR have been utilized for predicting the severity of COVID-19. NLR and PLR reflect systemic inflammation, neutrophil and platelet activation, and poor prognosis. Neutropenia results in a decrease in NLR, especially in mild cases, compared to controls. (Esmaeili & Esmaeili, 2025). In the present study, even though platelet counts decrease in cases, the magnitude of decrease in ALC is much more than that of the decrease in platelets, which results in increased PLR in cases compared to controls. PLR showed a gradual increase from mild to severe cases ($p<0.001$). This is in alignment with Fois et al., study that non-survivors have a higher PLR in comparison to the surviving COVID-19 patients (Fois et al., 2020).

In the present study, there was a steady increase in MLR ($p=0.03$). While a rise in MLR and PLR may suggest COVID-19 without pneumonia, a drop in total WBC, neutrophil, monocyte, and eosinophil levels supports the diagnosis of COVID-19 pneumonia (Koc et al., 2024). The patient may have a cytokine storm if platelets are remarkably increased, and the degree of cytokine storm is indicated by the level of PLR, which may offer a novel indicator for COVID-19 patients (Qu et al., 2020; Kosidło et al., 2023).

In the present study, SII and SIRI showed an initial decrease in mild cases compared to controls, then the levels increased, resulting in a statistically significant increase in moderate and severe cases. SIRI is better than SII in that the levels in severe cases were significantly higher than those in moderate cases. Thus, SIRI could differentiate severe from moderate cases of COVID-19 infection (Table 1). SIRI may also reflect the host's immune and inflammatory balance. The systemic immune-inflammation index (SII) is effective in reflecting inflammatory status, being a basic biomarker for predicting the prognosis (Moorthy et al., 2021; Citu et al., 2022).

Of all the inflammatory markers, SII may specifically reflect pulmonary damage in COVID-19 patients (Fois et al., 2020). Leukocyte, platelet, NLR and SII values may have a role in the diagnosis of COVID-19 (Usul et al., 2020). The individuals with a poor prognosis and high mortality have higher NLR, SII, and SIRI levels. SII and SIRI have better potential compared to NLR. This reflects the suppression of the inflammatory process mediated by monocytes and neutrophils. Positive clinical outcomes are linked to low SIRI and SII levels (Okuyan & Golen, 2022). According to Cakcak et al, SII is better than NLR, MLR, and PLR, and it comprehensively reflects the balance between the host immune status and the inflammatory condition (Cakcak et al., 2022).

In the present study, correlation analysis showed that inflammatory indices (NLR, SII, SIRI) were strongly intercorrelated and correlated positively with ANC and total leukocyte count, but negatively with ALC (Table 2). This is in alignment with the study by Karaaslan et al., which shows that SII exhibits a positive correlation with CRP, neutrophil, NLR, and PLR. The SII is a proinflammatory indicator of systemic inflammation that can be used to predict COVID-19 mortality (Karaaslan & Karaaslan, 2022). MLR demonstrates a high diagnostic value in distinguishing COVID-19 patients from healthy people. The ALC may help establish the early diagnosis of acute respiratory distress syndrome. MLR, NLR, and ALC could be quick, affordable, and promising markers to help with COVID-19 diagnosis, early warning, and risk assessment (Peng et al., 2020). PLR may be assessed in conjunction with other inflammatory indicators because it is higher in individuals with severe clinical conditions than in those with moderate ones (Qu et al., 2020).

ROC showed the highest AUC for NLR in both models. But AUC was elevated other markers in Model 2 which was adjusted for age, compared to Model 1. The cut-off values were higher in Model 2 compared to Model 1 (Table 4 and Figure 1).

When determining the severity of the disease course and choosing the best course of treatment, SII is helpful (Kosidło et al., 2023). In patients with confirmed COVID-19, CBC-derived inflammatory indices at hospital admission are predictive of poor outcomes. Patient survival is substantially connected with increases in NLR, PLR, MLR, SIRI, and SII from the cut-off values. CBC is a low-cost and easily accessible test for an early indicator of poor outcomes. It may be helpful for physicians and medical staff in resource-constrained nations to decide when to treat COVID-19 patients aggressively (Haryati et al., 2023). Non-invasive, readily accessible, and reasonably priced prognostic-predictive inflammatory indicators are SIRI and SII. More research is required to validate the results and pinpoint the underlying mechanisms, since it is crucial to know the precise mechanism of the inflammatory response in order to implement immunomodulatory therapy (Okuyan & Golen, 2022).

Table 4 shows the odds ratio of progression of the disease from mild/moderate to severe disease. Two models are shown here, first is unadjusted, second model is adjusted for age. NLR, PLR and SII showed 13.08, 8.59 and 9.88 times the risk of progression of the disease which were statistically significant. The risk based on SIRI was 3.76 which was much less than other markers, and also the significance decreased when adjusted for age. MLR did not show any signifcance OR with or without adjustment for age. (Table 4) A study by Cui et al. 2022, also showed that NLR and MLR are the best marker of indicating comapred to other markers. (Cui et al., 2022) The present showed in addition to NLR, other markers such as PLR, SII and SIRI were also indicators of risk for severe disease.

The study has included control individuals who were proven to be negative for COVID-19 infection by RT-PCR. The sample size for the cases was fairly adequate. Since the sample was relatively large, most of the statistical tools were applicable.

CONCLUSION

The study underscores the critical role of systemic inflammatory markers- NLR, SII, and SIRI- in assessing the severity of COVID-19. Elevated levels of these markers were significantly associated with severe disease, reflecting heightened immune activation and dysregulation. In particular, patients in their sixth decade of life exhibited severe clinical presentations, supporting the established correlation between age and COVID-19 severity. Thus, NLR showed excellent diagnostic accuracy, while SII provided good discrimination and high odds ratios, suggesting that simple CBC-derived indices can support risk stratification in resource-limited settings.

AUTHOR CONTRIBUTIONS

Ebezac Preetham and Jasmine Chandra conducted the experiments, analysed the experimental data, and drafted the manuscript. Umarani Saravanan contributed to data analysis and assisted in drafting the final version of the manuscript. Swathy Moorthy assisted in preparing the manuscript draft. Santhi Silambanan conceived and designed the study, managed the research, and drafted the final version of the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL

All the procedures performed in studies involving human participants were by the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional ethics committee approval was obtained (IEC-NI/20/AUG/75/49, dated 08-08-2020). Waiver of informed consent, as permitted by the national regulatory body was obtained as the patients were treated and discharged from the hospital. Patient identification was de-identified reversibly for the purpose of the analysis.

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Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

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