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Research

Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio as a predictor of mortality in severe COVID 19 cases

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Abstract

Background: With the periodic recurrence of Covid-19 waves affecting millions, there was an urgent need to identify accessible biological markers that could predict disease severity and mortality early in the illness. Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) have been proposed as potential inflammatory indicators for this purpose.

Methods: A retrospective cohort study was conducted on 224 Covid-19 patients (August–October 2020). Patients were categorized into 'mild' and 'moderate to severe' groups. Mann-Whitney U and Chi-square tests were used for continuous and categorical variables, respectively. Receiver Operating Characteristic (ROC) analysis determined cut-off values for NLR, PLR, and age, along with sensitivity, specificity, and likelihood ratios.

Results: Age, hemoglobin, and NLR were significant predictors of disease severity, with NLR showing the strongest association. Cut-off value of NLR > 4.24 demonstrated high sensitivity (88.3%) and specificity (82.6%) for severe disease. Cut off value of PLR > 165.63 also showed good predictive value. An NLR > 6 indicated increased mortality risk. Among those with NLR > 10, mortality was notably higher in the severe group.

Conclusion: NLR and PLR are valuable, low-cost prognostic markers for assessing Covid-19 severity and mortality risk, particularly in low-resource settings. Their use can aid early intervention and treatment decisions.

Keywords: COVID-19, Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), Disease Severity, Prognostic Markers, Mortality Prediction.

INTRODUCTION

Coronavirus disease 2019 (Covid - 19) is a viral illness which first began in Hubei province, China in November 2019. It was a rapidly spreading disease, involving millions of people – young and old, across all countries. The World Health Organization (WHO) declared it a global pandemic in March 2020. Since then, it infected millions of people across the globe with clear evidence of person –to-person transmission of the disease. Presentation of Covid - 19 varies widely among individuals, affecting the upper respiratory tract only in majority of cases, but in few cases like the elderly, unimmunized and immunocompromised individuals; it can progress to involve the lower respiratory tract, worsening to acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ dysfunction syndrome (MODS), and subsequent mortality[1].

Given the rapid disease transmission of the Covid - 19 virus affecting everyone from newborns to elderly, it was important to continuously improve and enrich its clinical diagnosis and treatment research. This includes good and quick laboratory results and characterising clinical features with improved precision and elucidating the risk factors associated with mortality. Studies have shown progression of the disease caused by inflammation. Severe inflammatory responses contribute to weak adaptive immune response, thereby resulting in immune response imbalance. Thus, circulating biomarkers can represent inflammation and immune status, which could be used as potential predictors for prognosis of Covid - 19 patients. Commonly calculated, Neutrophil-to-lymphocyte (NLR) ratio, platelet-to-lymphocyte (PLR) ratios were cheaply available indicators of systemic inflammatory response that can be widely investigated as useful predictors for the prognosis of patients with pneumonia [2].

Numerous studies using NLR, PLR ratios as predictors of mortality and morbidity in patients with cancer, cardiac disease and sepsis amongst other conditions have been published worldwide. Several studies have proposed that NLR, PLR ratios can be reliable predictor of Covid - 19 progression. This is a reliable, cost effective and easy to calculate laboratory marker [3]. There are very few studies documenting the role of NLR, PLR in Covid - 19 from this region. This is a study of NLR, PLR ratios and its association with severity of disease and treatment outcome from a tertiary care centre of south India.

MATERIALS AND METHODS

Study Design: Hospital based retrospective cohort
Study Setting: tertiary care centre and teaching hospital in South India, Karnataka
Study Population: Patients admitted with Covid -19 illness in the ward/ICU.
Study duration: 5 months, between August 1ST 2020 to October 31st
Sample Size: 224
Sampling method: Simple Random sampling
Case selection: All patients were selected based upon the inclusion and exclusion criteria as formulated below:

Inclusion criteria:

- All cases considered in the study were confirmed to be Covid - 19 positive with at least one nasopharyngeal swab positive for reverse transcription polymerase chain reaction (RT-PCR).

Exclusion criteria:

- Patients aged <18years.
- Patients who were referred from other centres after several days of hospitalization.

- Patients with solid malignancy on chemotherapy and hematological disorders like myeloma, leukemia and lymphoma.
- Patients with documented glucocorticoids exposure before admission.

METHODOLOGY

A total of 224 patients were consecutively enrolled in the study through purposive sampling were confirmed to be Covid - 19 positive with at least one nasopharyngeal swab positive for reverse transcription polymerase chain reaction (RT-PCR). The patients included in the study were diagnosed and classified into mild disease, moderate and severe disease based on the guidelines given by Minsitry of health and family welfare (MOHFW), Government of India and WHO [4].

Mild disease patients: Patients with fever, mild respiratory symptoms without shortness of breath or hypoxia, SpO2 > 94% or CT chest suggestive of mild Covid - 19 illness.

Moderate – severe disease patients: Patients with one of the following features:

a. Fever, respiratory tract symptoms (upper and lower)
b. Respiratory rate > 24cpm, breathlessness at minimal exertion or rest
c. SpO2 < 94% on room air, or requiring supplemental oxygen to maintain saturation (requirement of face mask, Non-Rebreather Mask, High-flow nasal cannula, Non-Invasive or invasive ventilation)

Patients not fulfilling the inclusion criteria were excluded from the study.

After obtaining consent from the patients, detailed clinical history, signs, data on comorbidities were collected from the patient or reliable attender. Peripheral venous blood samples were collected in EDTA and plain vacutainers on the first day of hospitalization. Hematological parameters like total leucocyte count, differential leucocyte count, platelet counts were measured using MindRay auto analyzer BC – 5380. Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) were calculated and noted. Their stay in the hospital along with treatment was closely followed up until discharge/death. Patients were classified into mild and moderate-severe as per MOHFW guidelines for classification of severity of Covid - 19 pneumonia.

In the study, values obtained were identified as continuous and categorical variables. Chi-square test was used for categorical variables and Mann-Whitney U tests was applied for continuous variables. ROC was plotted; sensitivity, specificity and likelihood ratios were calculated. Univariate analysis was performed using logistic regression analysis.

RESULTS

The total study population of 224 patients was divided into 2 groups (mild and moderate-severe) depending on the severity of the illness. The mild case group comprised of 122 subjects (54.22%) and the moderate-severe group consisted of 103 patients (45.7%). Among the 225 patients, 151 (67.11%) of the study patients were males and remaining were females. The mean age of the patients with mild severity was 40.12 ± 16.13 and that of moderate to severe group was 62.27 ± 13.88 years. The mean age of the patients with moderate-severe group was more than that of the patients with mild severity of Covid - 19 illness.

The laboratory indicators of the patients are also presented in Table 1. Patients in moderate-severe group had a higher leucocyte count of 10934 ± 6327.5 cells/mm^3 when compared to the mild severity group whose mean leucocyte count was 7797.5 ± 10986 cells/mm^3. About 45.7% of the patients had leukopenia with both the groups having normal platelet counts.

Logistic regression analysis showed age of the patient, NLR and PLR to be significant factors in determining the severity of the illness among patients which attained statistical significance, as shown in table 2. ROC curve analysis revealed NLR to be an excellent predictor of disease severity (sensitivity 88.30% and specificity 82.60%) at a cut-off of > 4.24 with corresponding positive and negative likelihood ratios being 5.07 and 0.24 as shown in table 3 and Figure 1.

ROC curve was drawn and AUC was also calculated for PLR and age of the patient, which revealed them to be good predictors of severity of illness in the patient. A cut-off of 165.63 was obtained for PLR, which showed a sensitivity of 69.90% and specificity of 61.20% with a positive likelihood ratio of 1.80 to predict disease severity. Age of 51.5 years was obtained as a cut-off, beyond which indicated increased severity of illness with a sensitivity of 77.70% and specificity of 79.30%. Predictive contributions of Age, PLR and NLR was quantified by their Z scores which showed NLR to be the strongest predictor of severity of illness in these patients, as shown in Table 3.

To further know the impact of NLR on serious clinical complication including mortality due to Covid - 19 illness, patients were further divided patients into two groups using NLR greater or lesser than 6 as the criterion to compared, therefore those patients who had NLR of greater than 6 were significantly higher rate of mortality as compared with those with NLR < 6 ($p < 0.001$). ROC analysis also predicted NLR to be an excellent prognostic marker for risk of death which showed (sensitivity 86.7% and specificity 84.4%) at a cut-off of > 6 as shown in figure 2 and Table 5,6.

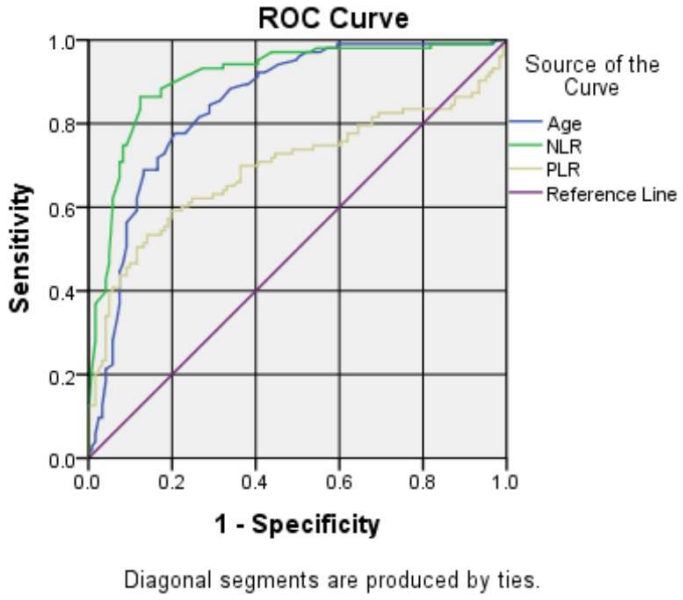

Fig 1: ROC curves of all variables (Age of the patient, NLR and PLR) in predicting severity of Covid - 19 illness among patients.

Table 1: The demographic details and clinical parameters of the studied patients

Characteristics	Mild cases (Mean±SD)	Moderate-Severe cases (Mean±SD)	P value
Number (n)	122 (54.2%)	103 (45.7%)	
Age (years)	40.12±16.13	62.67±13.88	*<0.001
Male	77 (63.6%)	74 (71.8%)	0.191

Female	44 (36.4%)	29 (28.2%)	
Laboratory parameters (median, IQR)			
Hemoglobin (Hb) g/dL	14.42±2.12	11.93±2.50	*<0.001
Total leucocyte count (TLC) number/mm3	7797.5±10986.6	10934.9±6327.57	*<0.01
Neutrophil (%)	70.72±11.99	88.46±7.74	*<0.001
Lymphocyte (%)	27.37±11.35	10.05±7.4	*0.001
Platelet count (Platelet) number/mm3	247280.9±73861.3	204914.5±96340.9	*0.003
Neutrophil-lymphocyte ratio (NLR)	3.61±3.34	14.31±12.35	*<0.001
Platelet-lymphocyte ratio (PLR)	167.57±90.81	311.10±242.39	*<0.001

Table 2: Association of NLR, PLR and Age of the patient with severity of the illness

Characteristics	Categories	Severity		Total	Odds Ratio	95% C.I.	P value
		Mild (N=121)	Moderate to severe (N=103)				
NLR	<4.2	93 (76.9%)	9 (8.7%)	102 (45.5%)	Ref.		<0.001
	≥4.2	28 (23.1%)	94 (91.3%)	122 (54.5%)	34.69	15.527 - 77.504	
PLR	<165.63	74 (61.2%)	31 (30.1%)	105 (46.9%)	Ref.		
	≥165.63	47 (38.8%)	72 (69.9%)	119 (53.1%)	3.657	2.094-6.387	<0.001
Age	<51.5 Yrs.	96 (79.3%)	23 (22.3%)	119 (53.1%)	Ref.		
	≥51.5 Yrs.	25 (20.7%)	80 (77.7%)	105 (46.9%)	13.357	7.048 - 25.313	<0.001

Table 3: Cut-off values obtained from ROC analysis for NLR, PLR and Age of the patient as predictors of severity of Illness.

Cut off values	NLR	PLR	Age (Yrs.)
	4.24	165.63	51.5
AUC	0.911, 95% C.I (0.871-0.951), p<0.001	0.695, 95% C.I (0.622-0.769), p<0.001	0.849, 95% C.I. (0.798-0.9), p<0.001
Sensitivity	88.30%	69.90%	77.70%
Specificity	82.60%	61.20%	79.30%
Positive Likelihood Ratio	5.07	1.80	3.75
Negative Likelihood Ratio	0.14	0.49	0.28

Table 4: Significant predictors of severity of Covid - 19 illness

	Odds ratio	C.I (95%)	p value	Z Score
Hb	.765	0.626-0.934	0.009	-2.629
Age	1.073	1.044-1.103	<0.001	4.977
NLR	1.356	1.216-1.512	<0.001	5.488

Table 5: Crosstabulation of NLR and impact of NLR cut-off value (6) on mortality in Covid - 19 illness

			NLR		Total
			less than 6	more than 6	
Group	Mild	Count	106	15	121
		% within Group	88.1%	11.9%	100.0%
		% within NL_C	86.7%	15.2%	55.5%
	Moderate and severe	Count	17	86	103
		% within Group	16.8%	83.2%	100.0%
		% within NL_C	13.3%	84.8%	44.5%
Total		Count	123	101	224
		% within Group	56.4%	43.6%	100.0%
		% within NL_C	100.0%	100.0%	100.0%

Table 6: Impact of NLT cut-off value (6) on mortality in Covid - 19 illness.

Statistics	Value	95% Confidence Interval
Sensitivity	86.72 %	79.59 % to 92.07 %
Specificity	84.85 %	76.24 % to 91.26 %
Positive likelihood ratio	5.72	3.57 to 9.17
Negative likelihood ratio	0.16	0.10 to 0.25
Disease prevalence	56.39 %	49.67 % to 62.94 %
Positive predictive value *	88.10 %	82.21 % to 92.22 %
Negative predictive value *	83.17 %	75.90 to 88.57 %
Accuracy *	85.90 %	80.69 % to 90.15 %

**These values are dependent on disease prevalence*

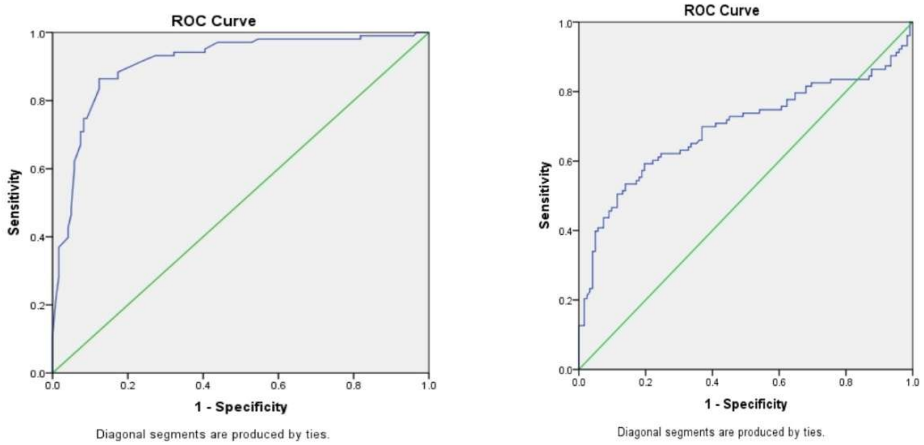

Fig 2: ROC curve of NLR (Cut-off 6) and PLR (cut-off 165.63) ratios in predicting mortality in Covid - 19 illness.

DISCUSSIONS

In this study, we conducted a retrospective cohort study to evaluate the predictive potential of NLR and PLR as a predictor of severity of disease and mortality among 225 Covid - 19 patients who were admitted to a

tertiary care centre in Mangalore, South Karnataka, India. Of the 225 patients studied, almost half of the patients (55%) had mild disease and the rest (47%) had moderate-severe disease.

Demographic data from our study showed that Covid - 19 patients who had severe Covid - 19 illness and mortality were significantly older compared to the ones with lower severity of illness and survivors. Similar to our reports, several reports from previous studies have showed that the severity of Covid - 19 illness was significantly related to age [5]. Studies in the western population however, showed no age difference between Covid - 19 patients in ICU and general population with mild infection suggesting that age alone is not a risk factor for ICU admission and to develop severe infection [6].

Regarding laboratory tests, several abnormalities have been reported in Covid - 19 patients like leucocytosis, lymphopenia and dysfunction in renal and liver parameters. Our data showed significant differences in the mean leucocyte count, lymphocyte and neutrophil counts between the mild and moderate-severe at the time of admission to the hospital. In severe Covid - 19 cases, the lymphocyte count decreases progressively while the neutrophil counts gradually increases. This may be due to the excessive inflammation and immune suppression caused by SARS-CoV-2 infection which triggers release of inflammatory markers such as IL-6 and IL-8 [7,8]. This also could have brought about changes in the NLR and PLR ratios. NLR is defined as the ratio between absolute neutrophil count/absolute lymphocyte count. Since the beginning of the pandemic, efforts have been made to search for ideal markers that can predict the severity and mortality due to the illness. NLR and PLR have been reported to prognosticate severity of the disease, mortality, days in ICU and days on ventilator stay [9,10]. We found significant difference in NLR levels between the mild and moderate-severe cases. Statistical significance was also found with age of the patient and PLR for the above two groups. The NLR ratios resulted from increased neutrophil count and reduced lymphocyte counts reflecting the changes between innate (neutrophil) and adaptive immunity (Lymphocytes). The increased NLR reflects dysregulated immune system. The overactive inflammatory responses in Covid - 19 illness leads to cytokine storm and worsen the tissue damage and triggers multi-organ failure which is one of the proposed pathogenesis related to the mortality in patients infected with Covid - 19.

Based on the ROC curve analysis, the optimal cut-off level for severity of the illness was 4.2 with a sensitivity of 88.3% and specificity of 82.6% which was in concordance with other national and international studies where the optimal cut-off ranged between 3.3 to 6.5 [11,12,13]. The difference in the cut-offs maybe due to the use of different dependent variables and study population. Optimal cut-off values may vary from one population to another and a lack of data on the reference range in a specific population may also explain these differences. Hence, determining the cut-off value is essential for NLR to be used in clinical settings specific to a specific locality [12]. Similarly, a cut-off for PLR of 165.3 was identified as an optimal cut-off value for severity of illness.

The current study identified the optimal cutoff level of NLR for mortality was 6, with a sensitivity of 86.4% and specificity of 84.8% which was comparable to studies done in China, Pakistan, Northern India. However, few previous studies done in China, Romania, Srilanka, parts of Africa recommended a higher cut-off for NLR with good sensitivity and specificity. This wide range of variability of NLR cut off between 6-12 is due to different conditions of patients, different study population and different comorbidities among the study population [12, 14-18].

The results in our study have several clinical implications and strengths. Our data confirms and expands the range of cut-off values used to predict severity and mortality of the disease. This predictive ability increases for a few days after admission when NLR reaches its peak, following which it tends to drop with recovery from

the illness. It also confirms and emphasizes the relevance of routine hematologic tests and provides a simple way, cheap and widely available test to determine the prognosis of the patients infected with Covid - 19 illness, which is conducive to the allocation of medical resources in our limited resource setup.

Limitations

With these notable advantages, the limitations in the study include,

- Due to single centre and just 224 patients in the study group, the real value of NLR and PLR might be underestimated or overestimated in predicting severity and prognosis of patients affected with Covid - 19.
- Confounders associated with the study included smoking, Body Mass Index, prior exposure to steroids, haematological malignancies, sepsis were unavoidable due to the retrospective nature of the study.
- NLR, PLR were analysed only at admission. However, there maybe need for serial monitoring of NLR, PLR throughout the disease course which could have been more specific in predicting mortality and severity of the disease.

CONCLUSIONS

High NLR, PLR and age of the patient, can be used as a predictive markers associated with the disease severity and mortality in Covid - 19 patients in our study. NLR is a simple, easily available, cost effective investigation which can be used as a risk stratification tool to identify patients with severe illness that helps in early decision making in patients management and judicious allocation of limited resources like oxygen support and ventilators, however further studies are required to validate this finding.

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