

## Original Research Article

# Study correlating lymphocyte to monocyte ratio and platelet to lymphocyte ratio with the severity in COVID-19 patients: a cross sectional study

Prabhu S., Nishant Patil\*

Department of General Medicine, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

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### \*Correspondence:

Dr. Nishant Patil,

E-mail: [nishantpatil183@gmail.com](mailto:nishantpatil183@gmail.com)

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## ABSTRACT

**Background:** The objective of this study was to classify COVID-19 patients into severe and non-severe groups and to correlate lymphocyte to monocyte ratio and platelet to lymphocyte ratio with the severity of COVID-19 patients.

**Methods:** It was a cross sectional observational study conducted on hundred patients admitted to Victoria hospital, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore between June 2020 and August 2020. Complete clinical data of the patients were taken and examined thoroughly and cases were diagnosed and severity was classified as per interim guidelines of World Health Organization (WHO) and diagnosis and treatment guidelines of COVID-19 by Ministry of Health and Family Welfare, Government of India. and compared and correlated with lymphocyte-monocyte ratio and platelet-lymphocyte ratio. A  $p < 0.05$  was considered significant. All analyses were performed using Statistical package for social sciences (SPSS) software version 10.

**Results:** The sample size in our study was 100 patients. The mean age of patients was 57.5 in severe and 35 in non severe COVID patients. Among these 67% were males and 33% were females. It was noted that, neutrophilia (median-88.5%) and lymphocytopenia (median-6.5) was seen among severe group. Also, the lymphocyte-monocyte ratio (LMR) was significantly low ( $p$  value-0.00\*) and platelet-lymphocyte ratio (PLR) was high ( $p$  value-0.00\*) and was statistically significant among severe COVID 19 patients.

**Conclusions:** LMR, PLR were significantly different between severe and non severe patients, so assessment of LMR, PLR may help identify high risk COVID 19 patients at an early stage. In our study LMR showed an acceptable efficiency to separate COVID 19 patients among severe and non severe group with a sensitivity of 82.4% and specificity of 84.8%. Whereas PLR showed high specificity of 93.9% and sensitivity of 64.7%

**Keywords:** COVID-19 patients, LMR, PLR

## INTRODUCTION

Coronaviruses are non-segmented positive-stranded RNA viruses with a roughly 30 kb genome surrounded by a protein envelope. Most coronaviruses cause diseases in their particular host species.<sup>1</sup> Those that can infect humans through cross-species transmission have become an important threat to public health. Two serious coronavirus disease outbreaks have happened in the past two decades:

severe acute respiratory syndrome (SARS) in 2003.<sup>2</sup> and Middle East respiratory syndrome (MERS) in 2012.<sup>3</sup> Since December, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recognized as the causal factor in a series of severe cases of pneumonia originating in Wuhan in Hubei province, China.<sup>4</sup>

This disease has been named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO).

SARS-CoV-2 has been shown to cause disease via a mechanism analogous to the SARS coronavirus, with potential damage to vital organs such as lung, heart, liver, and kidney, and infection poses a considerable risk to patients by the high prevalence of pneumonia.<sup>5</sup>

COVID-19 is responsible for wide range of clinical syndromes ranging from uncomplicated illness to severe pneumonia and acute respiratory depression syndrome (ARDS).<sup>6</sup> It would mainly depend on host inflammatory response, depending on excessive production of inflammatory cytokines such as IL-6 and TNF-alpha rather than direct virus-induced tissue damage.<sup>6</sup>

Since it is known that the function of whole immune system depends on the interaction between lymphocytes and macrophage system, a study is planned to analyse the lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) in predicting severity in COVID-19 infective disease.<sup>7-9</sup>

### ***Aims and objectives of the study***

To classify as non-severe and severe among Covid-19 patients. To correlate LMR and PLR with severity of COVID-19 disease.

## **METHODS**

### ***Inclusion criteria***

Age more than 18 years. Patients who tested RT PCR positive.

### ***Exclusion criteria***

Age less than 18 years. Pregnant women.

### ***Methodology***

The study is conducted in Victoria hospital, Department of medicine, Bangalore Medical College and Research Institute, Bangalore, which is a tertiary care centre in the region after obtaining approval and clearance from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled. Age less than 18 years and pregnant women were excluded from the study. The study was conducted for a period of 3 months, between June 2020 and August 2020. The imperative of informed consent is waived in light of the anonymous and observational character of this study.

Case record form with follow up chart were used to record the clinical data and examination, history of treatment and complications.

COVID-19 infection was diagnosed by RT-PCR technique. Patients underwent biochemical investigations which include complete blood count, liver function test, renal function test, serum electrolytes, serology. Co-

morbid conditions like metabolic disorders, endocrine disorders, renal disorders, cardiac disorders, respiratory disorders will be confirmed with past medical history.

Patients with complete clinical data were taken and cases were diagnosed and severity was classified on the basis of the interim guidance of the WHO and diagnosis and treatment guidelines of COVID-19, Ministry of Health and Family Welfare, Government of India. The Lymphocyte to Monocyte ratio and Platelet to Lymphocyte ratio was correlated with disease severity.

### ***Statistical analysis***

Statistical package for social sciences (SPSS) version 20. (IBM SPASS statistics (IBM corp. Armonk, NY, USA released 2011)) will be used to perform the statistical analysis.

Data will be entered in the excel spread sheet.

Descriptive statistics of the explanatory and outcome variables will be calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.

Inferential statistics like: Chi-square will be applied for categorical variables, non-parametric (Mann-Whitney) will be applied for non-normal distribution.

The level of significance is set at 5%. Any other necessary tests found appropriate will be dealt at the time of analysis based on data distribution.

## **RESULTS**

A total of 100 hospitalized patients with SARS COV-2 infection were included in the study. Among the study population, 66 patients fall in non severe COVID and 34 patients fall in severe COVID. The age distribution of the study population is as follows- 66 COVID patients who fell in the non severe group had a median age of 35 years and the remaining 34 COVID-19 severe patients had a median age of 57.5 years. The age between the two groups is significant (p value-0.00\*).

As in the Figure 1 shown below, clearly depicting that the severity of COVID 19 increases with increasing age as shown in this study (Figure 1).

In this study population, there were 67 males and 33 females, and 66 fall in non severe covid and 34 fall in severe COVID. Among non severe group (n=66), 63.6% (n=42) were males and 36.4% (n=24) are females. In severe group (n=34) 73.5% (n=25) were males and 26.5% (n=9) were females. As shown in figure 2, in our study population, the percentage of males were higher in both the severe and non-severe patients as compared to females showing a male predominance in a demographic picture.

In our study population, most common presenting symptoms were cough (42) followed by myalgia (30); fever (22); asymptomatic (16); shortness of breath (9); diarrhoea (9); sore-throat (6); anosmia (4); and rhinorrhea (1) (Figure 3).

As shown in (Figure 3), 58% of the study population (n=58) had no comorbidities at all. Out of the remaining

42% (n=42) of the population who had one or multiple comorbidities, hypertension and diabetes were the commonest. 66.6% (n=28) had hypertension followed by diabetes 40.4% (n=17), followed by chronic kidney disease 14.2% (n=6), ischaemic heart disease 7.1% (n=3), bronchial asthma 7.1% (n=3), malignancy 4.7% (n=2) and seizure disorder 2.3% (n=1) respectively.

**Table 1: Distribution of the subjects based on age.**

	N	Min	Max	Median	IQR	P value
Severe	34	34	80	57.5	20	0.00*
Non-severe	66	7	68	35	13	

**Table 2: Gender-wise distribution of the subjects.**

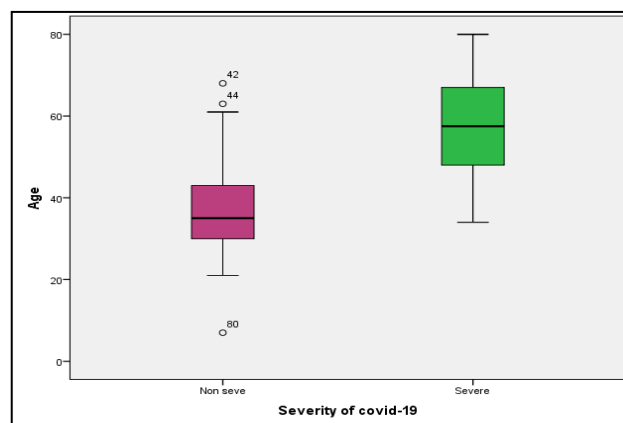
Gender		Severity		Total
		Non-severe	Severe	
Females	Count	24	9	33
	Percent	36.4	26.5	33
Males	Count	42	25	67
	Percent	63.6	73.5	67
Total	Count	66	34	100
	Percent	100.0	100	100
Chi-square value- 0.99				
P value- 0.31				

**Table 3: Severity of Covid-19**

		Non-severe (n=66)		Severe (n=34)	
		N	%	N	%
Hypertension	No	56	84.8	15	44.2
	Yes	10	15.2	19	55.8
Diabetes	No	61	92.4	22	64.7
	Yes	5	7.6	12	35.3
Chronic kidney disease	No	63	95.5	30	88.2
	Yes	3	4.5	4	11.8
Ischemic heart disease	No	66	100	31	91.2
	Yes	0	0	3	8.8
Bronchial Asthma	No	64	97	33	97
	Yes	2	3	1	3
Malignancy	No	66	100	32	94.8
	Yes	0	0	2	5.8
Seizure disorder	No	66	100	33	97
	Yes	0	0	1	3

In our study, the applicable thresholds for LMR and PLR were observed using the ROC curve. The optimum threshold at 2.1 for LMR showed a sensitivity of 82.4% and specificity of 84.8% and optimal threshold at 317.52 for PLR showed a sensitivity of 64.7% and specificity of 93.9%. Compared with patients in the non-severe group,

WBC count, neutrophil%, monocyte%, PLR were significantly higher in severe group, and lymphocyte%, LMR were Low in severe groups as compared to non-severe groups. While platelet count showed no significant difference between two groups.



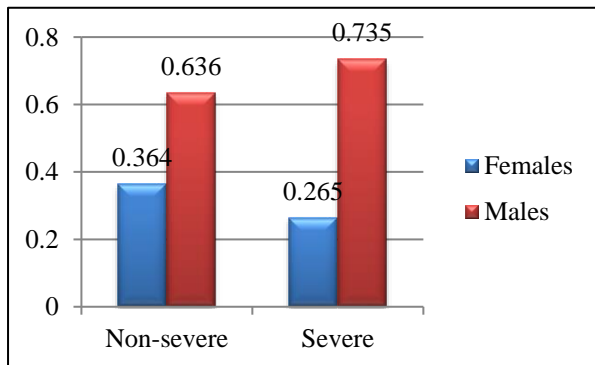
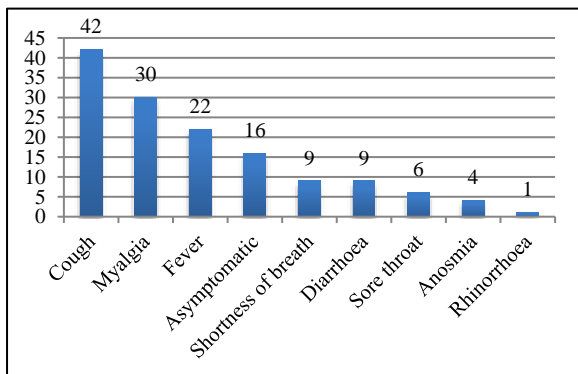
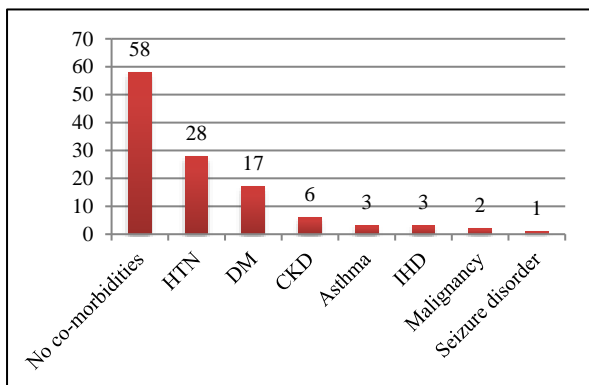
**Figure 1: Severity of Covid-19.**

**Table 4: Area under the curve of total WBC, neutrophil, lymphocyte, monocyte, platelet, LMR, PCR.**

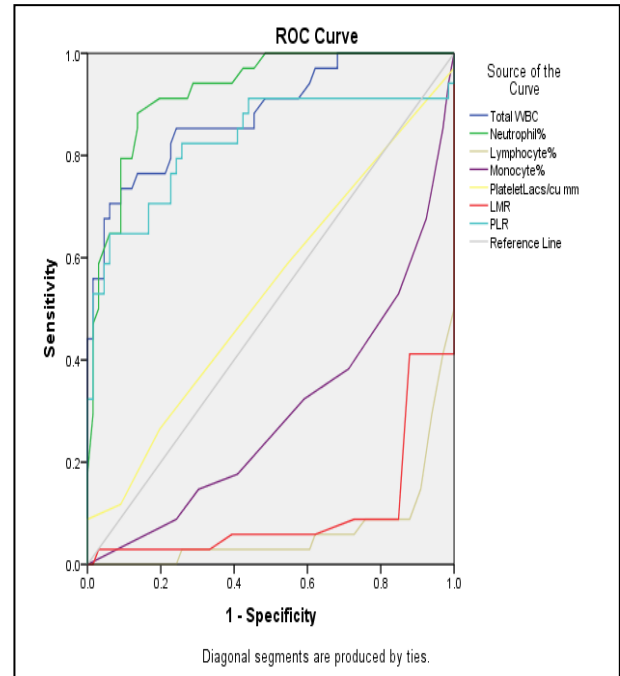
Variables	Area	P value	Asymptotic 95% CI	
			Lower bound	Upper bound
Total WBC	0.882	0.000	0.808	0.955
Neutrophil%	0.926	0.000	0.876	0.977
Lymphocyte %	0.065	0.000	0.011	0.119
Monocyte%	0.294	0.001	0.183	0.405
PlateletLacs/cu mm	0.533	0.593	0.410	0.656
LMR	0.101	0.000	0.028	0.174
PLR	0.828	0.000	0.726	0.929

**Table 5: Variable of total WBC, neutrophil, lymphocyte, monocyte, platelet, LMR, PLR.**

Variables	Cut off	Sensitivity (%)	Specificity (%)
Total WBC	12300	70.6	93.9
Neutrophil%	79	88.2	86.4
Lymphocyte%	13	91.2	87.9
Monocyte%	5	61.8	71.2
PlateletLacs/cu mm	2.89	0.5	66.7
LMR	2.1	82.4	84.8
PLR	317.52	64.7	93.9

**Figure 2: Gender wise distribution of the subjects.****Figure 3: Common presenting symptoms.****Figure 4: Distribution of co-morbidities among study population.**

Also, co-morbid conditions were found to be higher among severe population group as compared with non severe group (Table 3).i.e hypertension (55.8% versus 15.2%), diabetes (35.3% versus 7.6%), chronic kidney disease (11.8% versus 4.5%), ischemic heart disease (8.8% versus 0%), malignancy (5.8% versus 0%) respectively.

**Figure 5: ROC curve.**

## DISCUSSION

Patients with severe COVID-19 disease had low LMR and high PLR values when compared to non-severe disease. The present study shows that levels of LMR and PLR correlate with COVID-19 disease severity.

Patients with severe COVID-19 disease present with increased leukocytosis, neutrophilia, lymphocytopenia and monocytosis than those with non-severe disease.<sup>10</sup> These patients were more likely to develop ARDS and require intensive care unit (ICU) level of care.<sup>11-13</sup> LMR and PLR are easily obtained from a serum complete blood count with a differential profile. They serve as a function of relative neutrophilia, lymphopenia and monocytosis. The different mechanisms of lymphopenia in COVID-19 patients have been linked to the virus's ability to infect T-cells through the angiotensin-converting enzyme 2(ACE2) receptors and cluster of differentiation (CD)147-spike proteins.<sup>14,15</sup> The final results were decreased levels of CD3+, CD4+, CD8+ T lymphocytes, and increased regulatory T cells. The rise of pro-inflammatory cytokines with T cell lymphopenia predisposes severe COVID-19 patients to cytokines storm, thus resulting in more lymphocytic apoptosis and multi-organ failure. Overall, the decreased levels of CD4+ and CD8+ T lymphocytes correlated with disease severity, which can lead to low LMR and high PLR.<sup>16-18</sup>

In cases of other viral pneumonia like influenza, LMR also showed good sensitivity than individual levels of lymphocytes.<sup>19</sup> Similarly, PLR correlated well with mortality and disease severity in bacterial pneumonia.<sup>20</sup>

In a study done by Ghahramani et al which showed lymphopenia and monocytosis were found in severe patients as compared to non-severe patients which is correlated with our study.<sup>21</sup> Gomez et al in his study observed that during SARS-Cov-2 infection there are morphological and inflammation related phenotypic changes in peripheral blood monocytes that correlate with the patients outcome, suggesting that an excessive monocyte-macrophage activation may lead to subsequent respiratory failure in severe patients.<sup>22</sup>

In a study done by Peng et al which showed monocyte to lymphocyte ratio an acceptable efficiency to separate COVID-19 patients from healthy subjects but failed to rule out IP patients, which is in contrast to our study which showed an optimal threshold of 2.1 LMR with a sensitivity of 82.4% and specificity of 84.8% to differentiate among severe and non-severe groups among IP patients.<sup>23</sup>

Chan et al in his study showed that PLR was higher among severe COVID-19 patients as compared to non severe patients which is in correlation with our study.<sup>24</sup> The results of our study have several clinical implications and strength since LMR and PLR could be quickly calculated based on blood routine test on admission, so we should pay attention to these laboratory findings to identify high risk COVID-19 patients.

## CONCLUSION

This study establishes LMR and PLR as a reliable prognostic markers to differentiate severe versus non-severe disease in COVID-19 patients. Early recognition of the severe cases allows for early triaging and timely initiation of management.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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