Section: Anaesthesiology

Research

THE ROLE OF d-NLR, RDW AND PLR IN PREDICTING CLINICAL SEVERITY IN COVID-19 INFECTION: A SINGLE-CENTER, RETROSPECTIVE OBSERVATIONAL STUDY IN A TERTIARY CARE MEDICAL COLLEGE HOSPITAL IN CENTRAL KERALA

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Abstract

Background: The corona virus disease 2019 (COVID-19) caused by SARS-CoV-2 virus has been declared as a global pandemic by WHO. Various hematological parameters may be considered as useful prognostic indicators in COVID-19 infection. **Materials and Methods:** Age, neutrophil to lymphocyte ratio (NLR), derived-NLR (d-NLR), platelet to lymphocyte ratio (PLR) and red cell distribution width (RDW) of 266 laboratory confirmed COVID-19 patients, at the time of admission, belonging to clinical category B and C were recorded and compared in this single-center, retrospective observational study. The receiver operating characteristic (ROC) curve was applied to determine the thresholds for bio-markers and their prognostic values were assessed. **Result:** A statistically significant elevated NLR (P=0.001), d-NLR (P=0.001), PLR (P=0.001) and RDW (P=0.026) were noticed in Category C (severe) group when compared to Category B group. From the ROC curve, it was established that d-NLR, NLR and WBC count proved to be a fair distinguisher (area under the curve between 0.7- 0.8) in predicting the clinical severity in COVID-19 patients. NLR and WBC count was found to be having the highest sensitivity of 82%, while d-NLR proved to be highly specific. Elevated age was also significantly associated with illness severity (P=0.001). **Conclusion:** Elevated age, WBC count, NLR, d-NLR, RDW and PLR may be considered as useful prognostic biomarkers for predicting the severity of COVID-19 infection and adverse outcome, with NLR and WBC count showing the highest sensitivity and d-NLR with the highest specificity.

INTRODUCTION

In December 2019, several cases of new corona virus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) have been emerged from Wuhan, China,[1,2] which was later declared as a global pandemic by World Health Organisation (WHO) on March 11th 2020. Since then this infection has been spreading widely and rapidly, infecting more than 150 countries worldwide. As of May 8th 2022, over 514 million confirmed cases and over six million deaths have been reported globally.

WHO has broadly defined the clinical characterization of COVID-19 disease,[3] with most of the laboratory confirmed cases present with only mild to moderate symptoms. However, in some patients, a rapid deterioration of symptoms were noted, even leading to respiratory failure, septic shock or multi organ dysfunction, endangering life. Even after all these months, the early laboratory parameters which efficiently predicts the disease severity and outcome still eludes us. Early recognition of these laboratory indicators is important as it helps in delineating the severe patients from those with mild to moderate disease, which results in a rapid medical intervention,

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thereby decreasing the mortality rate as well as reducing the increased strain on the health care system especially in a developing country like India. The elevated levels of pro inflammatory cytokines, as seen during cytokine storm, is a characteristic feature of severe COVID -19 disease, causing Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Dysfuntion Syndrome (MODS), eventually leading to death in COVID -19 patients.[4] Hence, the many circulating inflammatory biomarkers may be used as significant predictors of disease severity and mortality in COVID- 19 patients. Several studies have been conducted during the last year to assess the predictive role of inflammatory markers such as peripheral white blood cell (WBC) count, neutrophil (NEU) to lymphocyte (LYM) ratio (NLR), derived NLR ratio (d-NLR) and platelet to lymphocyte ratio (PLR) in severe COVID -19 patients, in China and some European countries.[5,6,7,8] However, studies from the Indian subcontinent are very less. Hence, we designed this study to evaluate the accuracy of NLR, d NLR, PLR and RDW (red cell distribution width) in predicting the clinical severity in COVID-19 patients in Indian scenario.

MATERIALS AND METHODS

We conducted a single center, retrospective observational study on 266 laboratory confirmed COVID-19 cases, after obtaining the Institutional scientific and ethics committee approval. All these adult COVID-19 cases, confirmed by either Rapid Antigen test or TrueNat test or by RT-PCR test, of more than 18 years of age, of either sex, belonging to Category B or C [categorised as per our State treatment guidelines of COVID-19(Figure 1)], who were admitted in our hospital from September to December 2020, were included in our study and subsequent data collection and analysis. However, if any of the studied data was found missing or inadequate, those patients were excluded from further study and analysis. The need for informed consent was renounced, considering the retrospective, observational and anonymous nature of our study.

We performed a retrospective medical chart review method for data collection. A trained researcher, who was unaware of the study protocol obtained the epidemiological characteristics, clinical signs and symptoms as well as the laboratory investigation results especially complete blood count at the time of admission. A second researcher monitored all the collected data for analysis. From the obtained laboratory data, the parameters such as WBC count, NLR, d-NLR (neutrophil count divided by the result of white blood cell count minus neutrophil count), RDW and PLR were primarily studied.

The statistical analysis were performed using the software Statistical Package for the Social Sciences [SPSS] for Windows version 17.0 [SPSS Inc., Chicago, IL, USA]. Continuous data was represented as mean and standard deviation. Student t test or Mann–Whitney U-test was used for comparisons of quantitative variables among groups. Chi-squared test was performed to assess differences in proportions across groups. Area under the receiver operating characteristic curve (AUROC) were calculated and was used to compare the thresholds for bio markers and their diagnostic performance. P value < 0.05 was considered statistically significant.

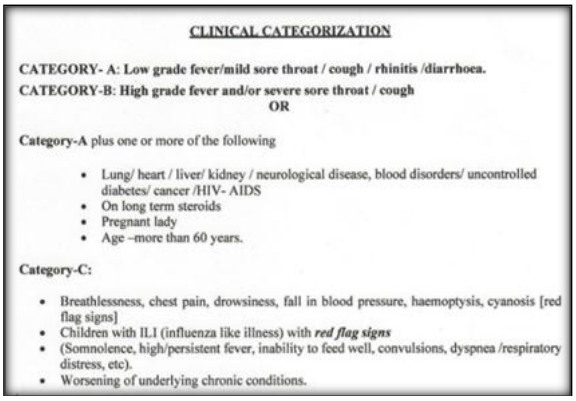

Figure 1: Clinical Categorization

RESULTS

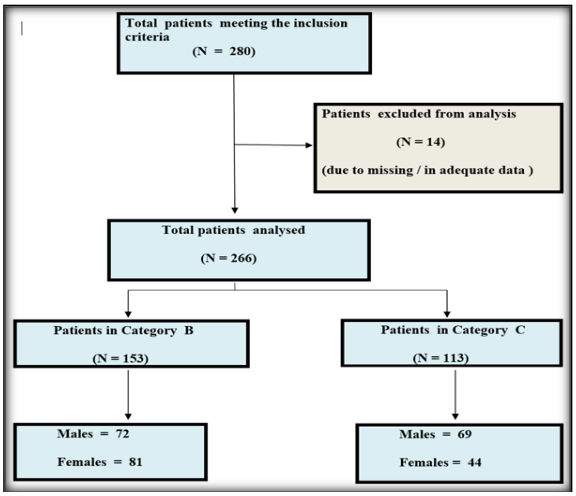

Figure 2: STROBE Flow Diagram

After meeting the inclusion criteria, we retrospectively reviewed the medical charts of 280 patients, who were admitted in our hospital during the study period. Among them 14 patients were excluded from further data analysis, due to either missing or inadequate data. The remaining 266 patients were included in our data collection and analysis in which 153 patients belonged to Category B, while 113 patients were included in Category C. [Figure 2]

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Table 1: Demographic and Laboratory Characteristics

	Category B (N= 153)	Category C (N= 113)	P value
Age (years)	51.85 (18.49)	63.52 (11.95)	0.001*
Sex (M/F)	72 / 81	69 / 44	0.024*
WBC count	7.49 (3.66)	9.99 (5.43)	0.001*
Neutrophil	67.67 (14.37)	81.64 (11.69)	0.001*
Lymphocyte	25.14 (13.01)	13.73 (10.41)	0.001*
Absolute Lymphocyte count	1.67 (1.00)	1.13 (0.94)	0.001*
Platelet count	234.39 (78.88)	233.02 (92.93)	0.897
NLR	4.68 (6.00)	11.81 (12.02)	0.001*
d-NLR	3.16 (3.14)	7.71 (8.09)	0.001*
PLR	188.96 (140.76)	307.67 (221.84)	0.001*
RDW-SD	42.66 (5.40)	44.26 (6.25)	0.026*
RDW-CV	14.11 (2.07)	14.35 (2.18)	0.369

Data expressed as Mean (standard deviation) or Number WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, d-NLR: derived-NLR, PLR: Platelet to Lymphocyte Ratio, RDW-SD: Red cell Distribution Width- Standard Deviation, RDW-CV: RDW- Coefficient of Variation
*significant at the 0.05 level

The demographic profile as well as the laboratory characteristics of the study participants are shown in the [Table 1]
The average age of the patients in our study was 56.82 years, with the maximum age recorded was 88 years. The average age of patients in less severe group (Cat B) was 51.85 years, while in severe group (Cat C) it was 63.52 years. Considering gender, a statistically significant increase in the number of male patients were noted in Cat C group (P= 0.024). The age, WBC count, NLR, d-NLR, and PLR in severely ill patients were significantly higher (P= 0.001) when compared to less severe group (Table 1). RDW-SD (red cell distribution width- standard deviation) also showed a statistically significant higher values (P= 0.026) in Cat C than in Cat B patients. While lymphocyte count was found to be significantly lower in Cat C group [Table 1].

Table 2: Area under ROC curve of WBC count, NLR, d-NLR, PLR and RDW-SD

Test Result Variable(s)	Area	Std. Error a	Asymptotic Sig. b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
WBC count	0.708	0.033	0.001*	0.643	0.773
NLR	0.769	0.030	0.001*	0.711	0.827
d-NLR	0.782	0.028	0.001*	0.726	0.838
PLR	0.690	0.033	0.001*	0.624	0.755
RDW-SD	0.594	0.036	0.009*	0.525	0.664

a Under the non-parametric assumption
b Null hypothesis: true area = 0.5
WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, d-NLR: derived-NLR, PLR: Platelet to Lymphocyte Ratio, RDW-SD: Red cell Distribution Width- Standard Deviation

Table 3: Category of Area under ROC curve (AUROC)

AUROC	Category
0.9 - 1	Very good
0.8 – 0.9	Good
0.7 – 0.8	Fair
0.6 – 0.7	Poor
0.5 – 0.6	Fail

Table 4: Coordinates of ROC curve

Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	1- Specificity
WBC count	6.045	0.825	0.497
NLR	3.067	0.823	0.399
d-NLR	3.008	0.743	0.268
PLR	164.320	0.717	0.418

WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, d-NLR: derived-NLR, PLR: Platelet to Lymphocyte Ratio

Table 5: Comparing Category B and C patients, when cut off for NLR is 3.3

NLR	Category B	Category C	P value
</= 3.3	93	24	0.001*
> 3.3	60	89	

Data expressed as number, NLR: Neutrophil to Lymphocyte Ratio
*significant at the 0.05 level

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Using the parameters that are found to be statistically significant, a ROC curve was plotted and AUROC was determined [Figure 3]. From the ROC curve, it was established that d-NLR, NLR and WBC count proved to be a fair distinguisher (AUROC between 0.7-0.8) in predicting the clinical severity in COVID-19 patients [Table 2-3]. NLR and WBC count was found to be having the highest sensitivity of 82%, while d-NLR proved to be highly specific (73%) with a sensitivity of 74% [Table 4]. A cut off value of 3.3 was taken for NLR from a previous study5 and on comparing with patients from Cat B and Cat C, a statistically significant increased number of patients was found in Cat C severe group with NLR values more than 3.3 at admission [Table 5].

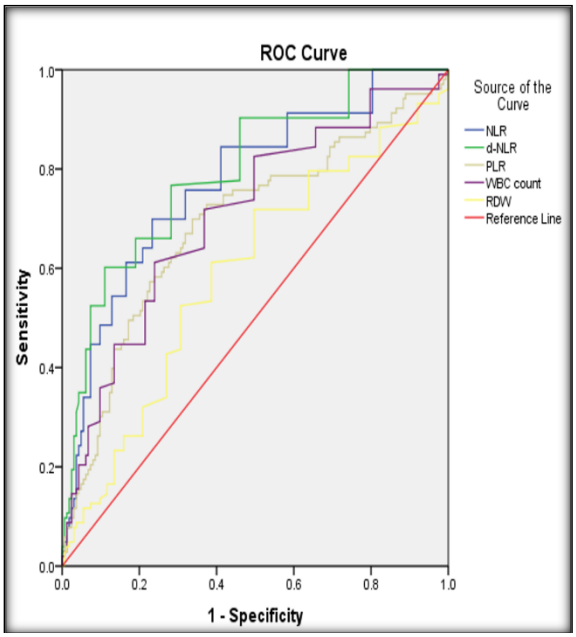

Figure 3: ROC Curve

DISCUSSION

Corona virus disease 2019 (COVID-19) is predominantly an infection of the respiratory tract caused by novel SARS-CoV-2 virus, which has been spreading worldwide fast and wide, ever since its first reporting from Wuhan, China in December 2019. Even though numerous studies on COVID-19 had been reported from different parts of the world, the studies from the Indian sub-continent are only a few. Hence, we conducted this study to evaluate the predictive role of NLR, d NLR, PLR and RDW in assessing the clinical severity in COVID-19 patients in India.

In our study, while studying the demographic characteristics, we found that more often males were severely affected when compared to females, similar to the findings of several previous studies on COVID-19.[9,10,11] Several studies on SERS COV and MERS also showed that males are more adversely affected than females.[12,13] In this study, the average age of patients in less severe group (Cat B) was 51.85 years, while in severe group (Cat C) it was 63.52 years, which showed a statistically significant increase in age in severe group, similar to the earlier done studies by Yang et al.5 and Maddani et al.[14]

Even though WHO has clearly and broadly defined the characteristic clinical features of COVID-19, a silhouette of the most illustrative laboratory abnormalities that were recorded in patients with COVID-19 is still elusive in the Indian scenario. In our study, we observed a statistically significant elevated levels of WBC count, NLR, d-NLR and PLR in severely ill group when compared to the less severe group. Also a statistically significant levels of neutrophilia as well as lymphopenia were recorded in Cat C severe group. RDW-SD values were also significantly high in Cat C group. From the ROC curve, d-NLR, NLR and WBC count proved to be a fair distinguisher in predicting the clinical severity in COVID-19 patients, with NLR and WBC count having the highest sensitivity of 82%, while d-NLR proved to be highly specific (73%) with a sensitivity of 74%.

The neutrophil to lymphocyte ratio (NLR) is a biomarker usually used for assessing the severity of bacterial infections as well as for predicting the prognosis of patients suffering from pneumonia, malignancy, auto immune diseases and tuberculosis. But in this COVID-19 times, NLR serves the purpose as a surrogate marker for early identification of disease severity in COVID-19 infection.[5,14,15] In our study NLR as well as d-NLR values were significantly elevated in severe illness group and therefore can be considered as an independent prognostic biomarker predicting the disease progression of pneumonia in COVID-19 patients. Yang et al.[5] while investigating and comparing 93 laboratory confirmed COVID-19 cases from Wuhan also obtained similar results, with a cut off value of 3.3 for NLR. We also observed a statistically significant increase in patients in critically ill group with NLR values more than 3.3. Earlier Forget et al.[16] had recorded that NLR values between 0.78 and 3.53 were normal in an adult, non-geriatric healthy population. Whereas, Jingyuan Liu,[17] concluded that COVID-19 patients with age ≥50 having NLR values ≥3.13 are at risk of advancing to severe illness, and they should be given priority to admission in the intensive care unit, if need arises.

The most relevant hematological abnormalities in COVID-19 patients are neutrophilia, lymphopenia and thrombocytopenia as it may effectively predict the morbidity and mortality in COVID-19. These prognostic indicators though they have its own definite clinical and biological importance but, when considered together, can even reflect the progression to more adverse clinical outcome.

COVID-19 patients exhibit significant neutrophilia. Neutrophil releases reactive oxygen species which

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results in cell DNA damage and therefore free the virus from cells. All these will stimulate cell-specific as well as humoral immunities. In addition to this, neutrophil releases numerous cytokines and effector molecules as they interact with specific cell populations, such as circulating vascular endothelial growth factor (VEGF).[18] VEGF usually stimulates growth, tumour angiogenesis as well as metastasis.[19] In COVID-19 patients, VEGF-A and VEGF-C have been shown to have a significantly higher expressions while comparing with normal tissues.[20] At the same time the reduced expression of VEGF and VEGFR results in profoundly inhibited organ and tissue damage.20 Also, virus-mediated inflammatory factors such as interleukin-6 and interleukin-8, granulocyte colony stimulating factor and tumor necrosis factor-alpha, and gamma interferons, produced by lymphocyte and endothelial cells, trigger the release of neutrophils.[21,22,23] Thus, virus-triggered inflammation resulting in neutrophilia and lymphopenia results in elevated NLR values. In COVID-19 patients with raised levels of NLR, the clinical symptoms were alarmingly severe with a rapid deterioration requiring mechanical ventilation and ICU care.

Lymphopenia, was shown as a hallmark feature of severe COVID-19 infection by Huang and Pranata.[24] Similarly Yang X et al.[25] specified in their article that lymphopenia was observed in 85% of the seriously ill COVID-19 patients. Chuan Qin et al.[26] in his study revealed that, primarily it is the dysregulation of the immune response, specifically of that of T lymphocytes, which are largely involved in the disease progression in COVID-19 infection. He also stated that even though inflammatory cytokines and infection induced biomarkers were significantly raised in most of the severely ill patients, T cells were significantly reduced.

The elevated PLR levels noticed in critically ill COVID-19 patients in our study may be related to cytokine storm,[7] which may contribute as a new indicator for the monitoring of disease severity in those patients. Meta-analysis on COVID-19 reported that both thrombocytopenia and lymphopenia were associated with severe COVID-19 infection.[24,27] However, the decrease in absolute lymphocyte count was much more pronounced than the decrease in the platelet count, thereby raising the PLR values. Simadibrata et al,[7] in their meta analysis on 998 COVID-19 patients also concluded that high PLR values were associated with COVID-19 severe infection. They postulated that cytokine storm activated by SARS-CoV-2 destroys the bone marrow progenitor cells, thereby reduce the synthesis of platelets. Also, the generation of autoantibody and immune complex instigated by SARS-CoV-2 cause the destruction of platelets, resulting in thrombocytopenia seen in critically ill COVID-19 patients.

In a recent paper, it is proposed that SARS-CoV-2 viral protein by the immune haemolysis of red blood cells infects hemoglobin, besides various mechanisms.[28] In our study we observed a statistically significant increase in RDW-SD in severe illness group when compared to less severe group which was in accordance to the findings obtained by Foy BH et al.[29] The reason for this elevated RDW seen in severe COVID-19 patients could be attributed to the suggestion from some previous reports on non-COVID-19 patients, that RDW can be raised when RBC production kinetics shows a slowing trend,[30] when there is elevated WBC and platelet kinetics.

There are a few limitation existed in our study. Firstly, we collected the data of the patients from a single research center, not from multiple centers. Secondly, due to time limitations we collected all the information only at the time of admission. There was no continuous follow up of the laboratory data. Also the sample size was small. Hence, for obtaining results with more accuracy, precision and external validity, a multi-centred clinical study with a larger sample size may be required.

CONCLUSION

Elevated age, WBC count, NLR, d-NLR, PLR and RDW may be considered as useful prognostic biomarkers for predicting the severity of COVID-19 infection and possible outcome, with NLR and WBC count showing the highest sensitivity and d-NLR with the highest specificity. Hence, in our setting, where scarcity of resources frequently prevent expensive testing, these prognostic biomarkers can be of extremely important, as they can help physicians to detect deteriorating cases early and to provide timely effective treatment, thereby reducing mortality in COVID-19 patients.

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