Original Research

Assessment Of Severity Of Covid-19 Vs D-Nlr And Rdw, Plr: A Retrospective Study Of Our Centre

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Abstract

Background: We know turnaround time for the complete blood count is much faster than that of various inflammatory markers like LDH, CRP, interleukins like IL-6, D-dimer. Thus using cell counts as a marker of severity and the prognosis is need of the hour. This will reduce the burden of the health care facilities. Complete blood count including the variation in RBC, WBC and platelets changes has been thoroughly studied. Various retrospective studies have shown that the absolute lymphocyte count can be taken as a marker of severity in COVID 19 patients. In December 2019, several cases of new corona virus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARSCoV-2) have been emerged from Wuhan, China, which was later declared as a global pandemic by World Health Organisation (WHO) on March 11th 2020.

Aim: In our study, we analyse and assess the severity of Covid-19 Vs d-NLR and RDW, PLR at our centre.

Method and materials: This is the retrospective observational study. We actually collected the data of 300 cases but out of 300 cases only 268 laboratory confirmed COVID-19 cases, Age, neutrophil to lymphocyte ratio (NLR), derived-NLR (d-NLR), platelet to lymphocyte ratio (PLR) and red cell distribution width (RDW) of 268 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.

Results and Observations: 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: COVID-19 is giving rise to tremendous challenges in the entire world and over pressurised the health care system and as of yet, efforts have been devoted to artificial intelligence based analysis of HRCT and x-rays have been used to indicate severity in the patients of SARS-CoV2. 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.

Keywords: Neutrophil to Lymphocyte ratio (NLR), derived-NLR (d-NLR), Platelet to Lymphocyte Ratio (PLR), Red cell Distribution Width (RDW), WBC count, COVID-19 Infection, Adverse outcome, Age, Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Dysfuntion Syndrome (MODS), COVID-19, SARS-CoV2.

INTRODUCTION

We know turnaround time for the complete blood count is much faster than that of various inflammatory markers like LDH, CRP, interleukins like IL-6, D-dimer. Thus using cell counts as a marker of severity and the prognosis is need of the hour. This will reduce the burden of the health care facilities. Complete blood count including the variation in RBC, WBC and platelets changes has been thoroughly studied. Various retrospective studies have shown that the absolute lymphocyte count can be taken as a marker of severity in COVID 19 patients. Lower absolute lymphocyte counts were found in severe patients who required high flow oxygen and intubation. Even, mortality rates were found to be higher in patients with lower absolute lymphocyte count **[1]**.

In COVID-19, neutrophils have been found in abundance, they found to be altered in phenotype and function. In initial phases of infection, local neutrophil in the nasopharyngeal epithelium is found to be elevated. Later in the course of disease, they are found to be higher in lung basal regions. Neutrophils are also found to be in higher concentration in blood circulation. Role of platelets in immune response of the body against any infection makes them an important immune cell. They have a role in hemostasis, coagulation, maintenance of vascular integrity, angiogenesis etc. Variety of cytokines like thrombopoetin interleukin 3,6,9,11 and stem cell factor promote the production of platelets from bone marrow.

There is alteration in activity and no. of platelets in various infections **[2].** In December 2019, several cases of new corona virus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARSCoV-2) have been emerged from Wuhan, China**,[3,4]** 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**,[5]** 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 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.**[6]** 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.**[7,8,9,10]** 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 COVID19 patients in Indian scenario.

Also some studies have shown that the total leucocyte count, absolute neutrophil count, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio were highest in the severely symptomatic group and lowest in the asymptomatic group. Neutrophil to lymphocyte ratio was positively associated with a risk of COVID-19 pneumonia **[11].** Severe disease was associated with significant neutrophilia and lymphopenia further intensified in critically ill patients**[12]**

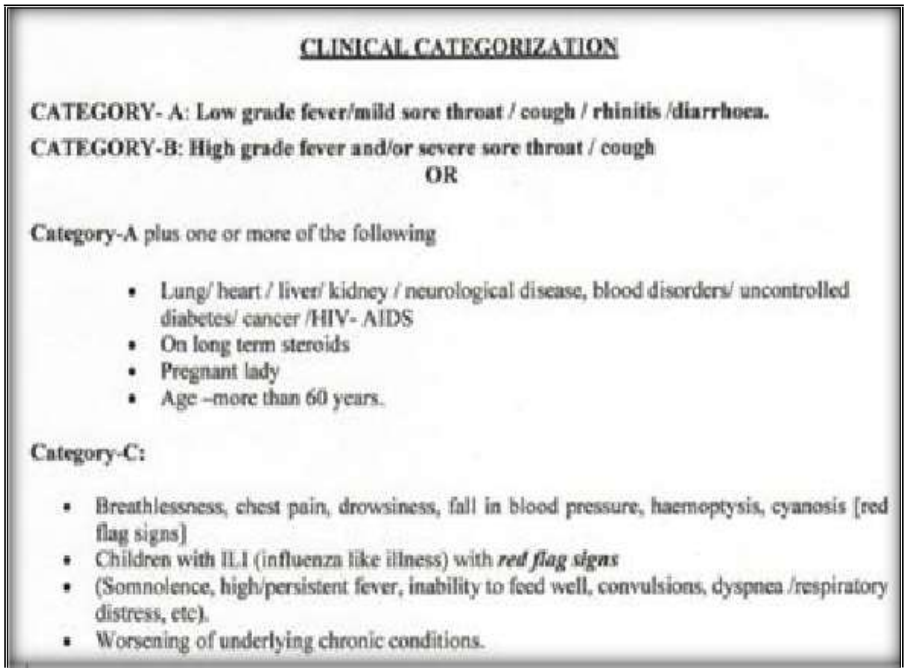
MATERIALS AND METHODS:

This is the retrospective observational study. We actually collected the data of 300 cases but out of 300 cases only 268 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.



CLINICAL CATEGORIZATION

CATEGORY- A: Low grade fever/mild sore throat / cough / rhinitis /diarrhoea.

CATEGORY-B: High grade fever and/or severe sore throat / cough

OR

Category-A plus one or more of the following

- Lung/ heart / liver/ kidney / neurological disease, blood disorders/ uncontrolled diabetes/ cancer /HIV- AIDS
- On long term steroids
- Pregnant lady
- Age –more than 60 years.

Category-C:

- Breathlessness, chest pain, drowsiness, fall in blood pressure, haemoptysis, cyanosis [red flag signs]
- Children with ILI (influenza like illness) with ***red flag signs***
- (Somnolence, high/persistent fever, inability to feed well, convulsions, dyspnea /respiratory distress, etc).
- Worsening of underlying chronic conditions.

Figure 1: Clinical Categories

RESULTS:

After meeting the inclusion criteria, we retrospectively reviewed the medical charts of 300 patients, who were admitted in our hospital during the study period. Among them 32 patients were excluded from further data analysis, due to either missing or inadequate data. The remaining 268 patients were included in our data collection and analysis in which 153 patients belonged to Category B, while 115 patients were included in Category C.

Table 1: Demographic Profile of the cases.

	Category B (N= 153)	Category C (N= 115)	P value
Age (years)	51.85 (18.49)	63.52 (11.95)	0.001*
Sex(M/F)	72 / 81	70 / 45	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.

Variables	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 Variables	Positive if >=	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	91	

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

Using the parameters that are found to be statistically significant, a ROC curve was plotted and AUROC was determined [Figure 2]. 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].

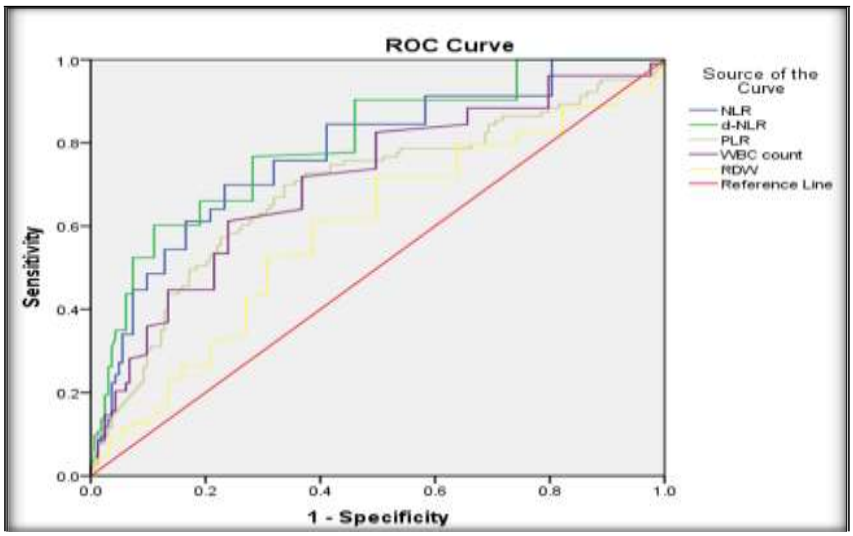


Figure 2: ROC Curve

DISCUSSION

Abnormal WBC morphology was more pronounced in monocytes and lymphocytes in milder form of disease; the changes were lost with disease progression. Higher RNA content in monocytes, lower RNA content in lymphocytes and smaller hypo-granular neutrophils were found **[13]**. 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**.[14,15,16**] Several studies on SERS COV and MERS also showed that males are more adversely affected than females.**[17,18]** 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.**[7]** and Maddani et al**.[19]** 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**.[19,20]** 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**.[7]** 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.**[21]** had recorded that NLR values between 0.78 and 3.53 were normal in an adult, non-geriatric healthy population. Whereas, Jingyuan Liu, **[22]** 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 results in cell DNA damage and therefore free the virus from cells. All these will stimulate cellspecific 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).[**23**] VEGF usually stimulates growth, tumour angiogenesis as well as metastasis.**[24]** In COVID-19 patients, VEGF-A and VEGF-C have been shown to have a significantly higher expressions while comparing with normal tissues.**[25]** At the same time the reduced expression of VEGF and VEGFR results in profoundly inhibited organ and tissue damage. Also, virusmediated 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.**[26,27,28]** 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.[**29]** Similarly Yang X et al.**[30]** specified in their article that lymphopenia was observed in 85% of the seriously ill COVID-19 patients. Chuan Qin et al.**[31]** 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,**[9]** 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 COVID19 infection**.[29,32]** 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, **[9]** in their meta analysis on 998 COVID-19 patients also concluded that high PLR values were associated with COVID19 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.**[33]** 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.**[34]** 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,**[35]** 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. Thrombocytopenia has been found

in both mild and severe disease, but mostly trend is towards normalisation of platelet count in the survivors. In non survivors and those with severe disease, platelets count are seen to be declining probably due to their increased production that is from megakaryocytic precursors and consumption at the site of infection that is the basal parts of lungs. Reduced production, increased destruction and enhanced consumption of platelets at the site of injury have been put forward. According to a paper, a value of 2.8 for NLR and 180 for PLR seem to be suggestive for COVID-19 and eosinophils=0.15 **[36].**

Conclusions:

COVID-19 is giving rise to tremendous challenges in the entire world and over pressurised the health care system and as of yet, efforts have been devoted to artificial intelligence based analysis of HRCT and x-rays have been used to indicate severity in the patients of SARS-CoV2. 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 dNLR 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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