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DATA ANALYSIS OF LABORATORY FINDINGS AND ITS USE IN PREDICTING REQUIREMENT OF OXYGEN IN A COVID 19 POSITIVE PATIENTS AT TERTIARY CARE HOSPITAL IN PUNE MAHARASHTRA.

Pathology

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ABSTRACT

INTRODUCTION: The coronavirus disease 2019 (COVID-19) is caused by the virus SARS-CoV-2 and is declared as a global pandemic by the World Health Organization (WHO). There are many western and Chinese studies have done, but there is a need for research to evaluate the pattern of the haematological parameters of COVID-19 patients & predict requirement of Oxygen in the Indian population.

MATERIALS AND METHODS: A retrospective cross sectional study carried out on 150 COVID-19 positive patients admitted form 1st May 2021 to 14th May 2021 in a tertiary care hospital, Smt. Kashibai Navale Medical College & General Hospital, India.

RESULTS: The final study population consisted of 150 patients. The Derived NLR and NLR & CRP had higher specificity and positive predictive value. The accuracy of Derived NLR, NLR and CRP was 66%, 64% and 63% respectively. The area under the ROC Curve (AUC) values of Derived NLR, NLR, and CRP indicates that there was a 65% probability that these significant indicators were able to distinguish patients required oxygen or not (on room air).

CONCLUSION: History of Diabetes, hypertension plays measure role as a prognostic factor in a COVID 19 Positive. But other hematological parameters like NLR, derived NLR, CRP ferritin also plays measure role in predicting requirement of oxygen.

KEYWORDS

INTRODUCTION

In China, in November 2019, Wuhan city reported several cases of unexplained viral pneumonia. After a throat swab examination, (CCDC), the Chinese Centre for Disease Control and Prevention, confirmed Novel Corona Virus. [1] WHO named it Corona Virus Disease in January 2019. Since it spreads to other countries and worldwide and become sever health issue.(2) Diagnosis of COVID-19 is typically performed using polymerase chain reaction testing via nasopharyngeal swab.(3) COVID 19 infection may be asymptomatic, or it may cause a wide spectrum of symptoms, such as fever, dry cough, and shortness of breath. COVID-19 severity can also progress to severe and eventually critical conditions defined by respiratory failure, septic shock, and/or multiple organ dysfunctions.(4)(5) It is therefore of paramount importance for clinicians to establish reliable predictors of the progression of this illness for timely clinical/therapeutic decision-making. Common laboratory abnormalities among hospitalized patients include lymphopenia, elevated inflammatory markers (e.g. erythrocyte sedimentation rate, C-reactive protein, ferritin, tumour necrosis factor-α, IL-1, IL-6), and abnormal coagulation parameters (E.g. prolonged prothrombin time, thrombocytopenia, elevated D-dimer, low fibrinogen). However, there is a need for research to evaluate the pattern of the hematological parameters of COVID-19 patients in the Indian population. (6)(7)(8)(9)(10)

Government of India Ministry of Health and Family Welfare Directorate General of Health Services releases a guideline to classify and manage the COVID 19 positive patients in India. According to version 3, a patient who required Oxygen in any form to maintain SpO2 94% and above is classified as moderate to severe cases and need to be treated at a dedicated COVID centre. Those, who are maintaining, SpO2 94 % and above are categorized as mild cases.(11)
In the present study, we aimed to study the hematological parameters in COVID-19 patients, which include hemoglobin, Platelet count, Total leukocyte count, differential count, Neutrophil: Lymphocyte ratio (NLR), Lymphocyte: Monocytes ratio, Platelet: Lymphocyte ratio (PLR) in patients on room air and patients required Oxygen to maintain SpO2 94 % or above.

OBJECTIVES

1. To study the hematological parameters which include hemoglobin, Platelet count, Total leukocyte count, differential count, Neutrophil: Lymphocyte ratio (NLR), Lymphocyte: Monocytes ratio, Platelet: Lymphocyte ratio (PLR)
2. To observe the correlation between various hematological parameters and serum level of ferritin, D-Dimer, and CRP inpatient on oxygen and room air.

MATERIALS AND METHODS-

Study Design-

A retrospective cross sectional study carried out on 150 COVID-19 positive patients admitted form 1st May 2021 to 14th May 2021 in a tertiary care hospital, Smt. Kashibai Navale Medical College & General Hospital, India.

Including Criteria-

The positive cases of COVID-19 by RT-PCR admitted in dedicated covid19 ward during time period 1st may 2021 to 14th may 2021, were included in the study.

Patient required Oxygen to maintain SPo2 94 and those don't require Oxygen to maintain Spo2 equal or above 94 are also included in study.

Excluding Criteria -

Patients with chronic lung diseases, hematological disorders and malignancy on treatment were excluded from the study.

Procedure:

We divided COVID – 19 positive patients who passed inclusion criteria into two groups i.e. Oxygen and on Room air patients.

Patient who were COVID 19 RTPCR test positive and able to maintain SpO2 above 94, are covered under title on Room Air. Those Patient who are COVID 19 RTPCR positive but not able to maintain SpO2 below 94 and required Oxygen to maintained Spo2 94 are considered patient on Oxygen. In this study, for both on Oxygen and on Room air

patients, the first blood sample collected for obtaining the hematological parameters was considered and compared for statistical analysis.

CBC was done on 7-part hematological analyzer (Beckman Coulter). It includes following parameters with their respective cut-off values: Hemoglobin: 13.5 – 17.5 g/dl (male) and 12.0 – 15.6 g/dl (female); Platelet count: 1.5 – 4.5 lakh/ cumm; Total WBC count: 4,000 – 11,000/cumm, Absolute neutrophil count (ANC):1,500- 8,000/cumm; Absolute lymphocyte count (ALC):1,000 – 4,800/cumm; Neutrophil count: 55-70%; Lymphocyte count: 20-40%; Eosinophil count: 0-6%; Monocyte count: 0-7%. Neutrophil lymphocyte ratio (NLR) was calculated by taking the ratio of absolute neutrophil count to absolute lymphocyte count with cut-off < 3.13. Platelet Lymphocyte ratio (PLR) was calculated by taking the ratio of platelet count to absolute lymphocyte count with cut-off <180. Peripheral blood smears were stained by Ramanowasky satins to study the Red blood Cells and Platelets morphology. These parameters were assessed and compared in both the groups .i.e. those on Oxygen and those on room air.

Statistical Analysis:

We examined various ratios having prognostic values that are presented in the following Table 1. We collected the laboratory records of each patient and screened them to match the study criteria. Our findings are presented as mean, median, standard deviation, and range values for each continuous variable and as frequencies and percentages for categorical variables. We applied an unpaired t-test to compare the mean of continuous variables between two groups. We used the chi-squared test to examine the association between categorical variables. In addition, we applied a univariate binary logistic regression model to compute the odds of the requirement of oxygen in patients (an event) using prognostic markers. Finally, we performed diagnostic validity tests to assess the adequacy of each biomarker. We used receiver operating characteristics (ROC) curves to compare the different parameters. The ROC is a plot of sensitivity on the y-axis against (1-specificity) on the x-axis for varying values of prognostic markers. We analyzed the data in STATA 14 and considered a p-value 0.05 as statistically significant.

Table 1: Computation of prognostic markers

Parameter	Acronym	Formula
Derived neutrophil to lymphocyte ratio	**Derived N/L**	(Absolute neutrophil count)/(total leukocyte count – absolute neutrophil count)
Neutrophil to lymphocyte ratio	**N/L**	(Absolute neutrophil count)/(absolute neutrophil count)
Lymphocyte to monocyte ratio	**L/M**	(Absolute lymphocyte count)/(absolute monocyte
Platelets to lymphocytes ratio	**Plt/L**	(Absolute platelet count)/(absolute lymphocyte count)
CRP (mg/l)	**CRP**	serum C-Reactive Protein Level
D-dimer (µg/ml)	**D-dimer**	Serum D-dimer Level
Ferritin (ng/ml)	**Ferritin**	Serum ferritne level

RESULTS:

Table 2: Bivariate analysis of demographic characteristics and comorbidities of patients required oxygen and on room air (N = 150)

Demographic characteristics		Patients		Test of significance
		On room air (N = 32)	Required Oxygen (N = 118)	
Age (in years)		51.88	53.35	t = -0.4953; p-value = 0.6211 (NS)
Sex	**Male**	19 (19.8%)	77 (80.2%)	χ^2= 0.3777; p-value = 0.539 (NS)
	Female	13 (24.1%)	41 (75.9%)	
Diabetic Mellitus	**No**	29 (22.3%)	101 (77.7%)	χ^2 = 0.5516; p-value = 0.458 (NS)
	Yes	3 (15%)	17 (85%)	
Hypertension	**No**	25 (20.5%)	97 (79.5%)	χ^2 = 0.2758; p-value = 0.599 (NS)
	Yes	7 (25%)	21 (75%)	
N: Number; NS: Not significant				

Usually, the mean age of patients who required oxygen was slightly higher than those on the room air, but the difference was not statistically significant (p-value > 0.05). Similarly, the oxygen requirement was higher among male patients and patients with a history of diabetic mellitus and hypertension. But their association was statistically insignificant (p-value > 0.05). The mean age in our study was 53.03 years (SD: 14.88) of the patients. The patients included 64% males and 36% females. A little less than four-fifth of patients (79%) required oxygen, the remaining one-fifth (21%) were on room air. While about 13% of patients had a history of diabetic mellitus, 19% had a history of hypertension.

The various cell lines included in the computation of prognostic parameters are TLC, Platelets, Absolute neutrophil count , Absolute lymphocyte count , absolute monocyte count examined in the study. The mean TLC was 8786.63 (SD: 5134.66) cells/cumm, and the mean platelet count was 2.22 lac/cumm (SD: 0.95). The mean values of absolute neutrophil, lymphocyte, and monocyte counts were 80.35% (SD: 10.36), 15.29% (SD: 9.26), and 3.49 (SD: 1.41) respectively.

Table 3: Comparison of test parameters between patients on room air and required oxygen (N = 150)

Parameter	Patients on room air (N = 32)		Patients required oxygen (N = 118)		t-test value
	Mean	S.D.	Mean	S.D.	
Derived N/L	4.21	2.83	6.53	4.79	t = -2.6130; p-value = 0.01 (HS)
N/L	5.77	4.12	9.49	8.02	t = -2.5348; p-value = 0.01 (HS)
L/M	5.03	2.47	4.39	2.55	t = 1.2631; p-value = 0.2085 (NS)
Plt/L	0.16	0.11	0.25	0.22	t = -2.2063; p-value = 0.01 (HS)
CRP (mg/l)	39.38	31.29	54.96	30.45	t = -2.5525; p-value = 0.006 (HS)
D-dimer (µg/ml)	2.98	5.32	1.57	3.24	t = 1.8773; p-value = 0.0312 (S)
Ferritin (ng/ml)	314.06	270.86	441.45	303.84	t = -2.1503; p-value = 0.02 (S)
N: Number; HS: Highly significant; NS: Not significant; S: Significant					

Table 3 shows the comparison of test parameters between patients on room air and required oxygen. The patients who required oxygen had a statistically higher Derived NLR, NLR, PLR, CRP, and Ferritin values while lower D-dimer value (p-value < 0.05).

Table 4: Ratio wise distribution and their significance in differentiating the patients by oxygen requirement

Test parameter	Cut-off value	Patients on room air (N = 32)		Patients required oxygen (N = 118)		Patients on room air vs. patients required oxygen		Odds ratio (95% CI)
		Number	%	Number	%	χ^2	p-value	
Derived N/L	< 4.72	23	30.67	52	69.33	7.7860	0.005 (HS)	3.24 (1.38 - 7.60)
	4.72	9	12.00	66	88.00			
N/L	< 7	22	28.95	54	71.05	5.3217	0.021 (S)	2.61 (1.14 – 5.98)
	7	10	13.51	64	86.49			
L/M	< 4	14	20.59	54	79.41	0.0411	0.839 (NS)	0.92 (0.4 – 2.02)
	4	18	21.95	64	78.05			
Plt/L	< 0.16	20	26.67	55	73.33	2.5424	0.111 (NS)	1.91 (0.86 - 4.26)
	0.16	12	16.00	63	84.00			
CRP (mg/l)	< 54.80	18	30.00	42	70.00	4.4756	0.034 (S)	2.33 (1.05 – 5.15)
	54.80	14	15.56	76	84.44			
D-dimer (µg/ml)	< 0.83	15	20.00	60	80.00	0.1589	0.690 (NS)	0.85 (0.39 – 1.86)
	0.83	17	22.67	58	77.33			
Ferritin (ng/ml)	< 312	19	28.36	48	71.64	3.5605	0.059 (NS)	2.13 (0.96 – 4.72)

	312	13	15.66	70	84.34			
N: Number; HS: Highly significant; NS: Not significant; S: Significant								

The correlation of the prognostic parameters with oxygen requirement is shown in Table 4. A suitable value closed to a median of each parameter is considered the cut-off value that showed high sensitivity and accuracy in predicting an oxygen requirement in patients. The Derived NLR, NLR, and CRP based on cut-off values were statistically associated with oxygen requirement in patients (p-value < 0.05). The patients whose Derived NLR was greater than or equal to the cut-off value were 3.24 times (95% CI: 1.38 – 7.60) more likely to require oxygen than those whose Derived NLR was lower than cut off value. The odds of oxygen requirement was 2.61 times (95% CI: 1.14 – 5.98) higher among patients having NLR greater than or equal to cut-off value than those with NLR lower than cut-off value. The patients who had CRP greater than or equal to the cut-off value were 2.33 times (95% CI: 1.05 – 5.15) higher as likely as their counterparts to require oxygen.

Table 5: Diagnostic validity tests for predicting Oxygen requirement in patients using various significant parameters

Parameters	Derived N/L	N/L	L/M	Plt/L	CRP (mg/l)	D-dimer (µg/ml)	Ferritin (ng/ml)
	< 4.72	**< 7**	**< 4**	**< 0.16**	**< 54.80**	**< 0.83**	**< 312**
Sensitivity	56%	54%	54%	53%	65%	49%	59%
Specificity	72%	69%	44%	62%	56%	47%	59%
Positive predictive value	88%	87%	78%	84%	84%	77%	84%
Negative predictive value	31%	29%	21%	27%	30%	20%	28%
Accuracy	66%	64%	64%	63%	63%	58%	59%

Using ROC curves, the diagnostic test validity of Derived NLR, NLR, LMR, Plt/LR, CRP, D-dimer, and Ferritin was analyzed using for predicting an oxygen requirement in patients (Table 5 and Figure 1). The Derived NLR and NLR had higher specificity and positive predictive value. At the same time, CRP had a higher sensitivity and higher positive value. The accuracy of Derived NLR, NLR and CRP was 66%, 64% and 63% respectively. The area under the ROC Curve (AUC) values of Derived NLR, NLR, and CRP indicates that there was a 65% probability that these significant indicators were able to distinguish patients required oxygen or not (on room air).

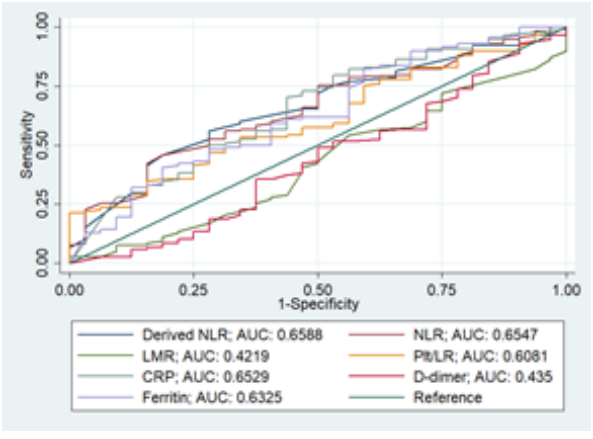

Figure 1: ROC curve and area under the ROC curve (AUC)

DISCUSSION

Many studies on COVID 19 are done after its breakdown and tried to find out correlation and prediction of various laboratory values in a covid 19 positive patients. When we compared our study with them, the mean age of the patient in our study was 53.03±14.88 years. Piyush et al. (6) Found in COVID 19 positive patients and admitted to ICU have a mean age of 52.4, whereas those with Non-ICU have a mean age of 38.8 years. J. Fu, et al.(5) in their study found in COVID 19 positive patients mean age 46.6 ± 14 years.

In our study, 78 % of cases were having Diabetic Mellitus and 18 % of patients were having Hypertension. A study done by BG et al. (9) Showed 36 % of patients having diabetic Mellitus and 24% of patients were suffering from Hypertension. Jain et al. (11) Found 25 % diabetic Mellitus patients and 27% Hypertensive cases in their study on COVID 19 positive patients.

The distribution of comorbidities, such as DM and HTN, and advanced age were significantly higher in the severe group, owing to them being independent risk factors for severe disease. (11) In our study, oxygen requirement was higher in diabetic and hypertensive patients.

The mean TLC (total leukocyte count) in our study was 8786.63/ cumm. A study done by Jain et al (11) showed mean TLC 6,717 ± 2,910.

In our study patient with raised derived NLR ratio, NLR ratio and LMR ratio required Oxygen. The area under ROC Curve (AUC) values of these ratios also indicates that there was a 65 % probability that these significant indicators were able to distinguish patients required oxygen or not.

The value of AUC in the Derived NLR ratio was 0.6588, and for NLR ratio was 0.6547. The value of AUC in PLR was 0.6081 in the current study.

The value of AUC for NLR & PLR were 0.779 and 0.668, respectively, in a study done by Jain et al. (11)they also stated that these values are important to predict the severity of disease in COVID 19 Positive patient.

Piyush et al. (6) also stated that NLR was significantly raised in ICU patients as compared to Non-ICU patients, proving it to be a valuable severity indicator.

The ratio of Platelet count to absolute lymphocyte count was not found to be having a significant difference, in a study done by Piyush et al.(6) However, as the platelets are dynamic parameter, the relevance of PLR can only be interpreted if follow up samples at different time points are taken.

It is shown by various studies, that serum ferritin, D-dimer and CRP values are increased in severe COVID 19 positive cases. (3)(5) (12).In our study also we found that patient required Oxygen are having raised values. Out of these CRP values more Sensitive and Specific in our study.

CONCLUSION

The confirmatory diagnosis of COVID-19 requires RT-PCR analysis, which is a time-consuming and less accessible test. To summarize, derived NLR, NLR,& CRP can help predict COVID-19 severity & oxygen requirement in our country, especially in resource-limited settings where sophisticated biochemical markers might not be easily available. With the use of the ROC curve, we provided the cutoff for these parameters, which can classify the patients into severe (required Oxygen) and non-severe (on Room Air) categories. This cutoff for derived NLR was 3.24, for NLR was 2.16, and for CRP were 2.33.

Conflict of Interest:
The authors declare no conflict of interest.

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