


## Correlation of refractory hypoxemia with biochemical markers and clinical outcomes of COVID-19 patients in a developing country: A retrospective observational study

### Running head: Predictors of hypoxemia in COVID-19.

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#### ABSTRACT

**Introduction:** COVID-19 is mainly a respiratory illness, causing hypoxemia in the majority of those been infected. In our study, we aimed to correlate the biochemical markers with hypoxemia and predicting the prognosis of COVID-19 patients.

**Materials and methods:** A retrospective, observational study was conducted to include all the admitted COVID-19 patients (n = 183) diagnosed by a real-time Polymerase chain reaction and evaluated those for hypoxemia and disease outcomes by utilizing the biochemical markers.

**Results:** Out of the 183 patients, 117 were in the ward, 66 were in ICU, 148 of them recovered, while 35 deaths were reported, 89 patients were having persisting hypoxemia (despite oxygen therapy) during the hospital stay, and the remaining 94 were non-hypoxemic with or without supplemental oxygen therapy. There were significant differences in mean hemoglobin (p = 0.028), total leukocyte count (p = 0.005), Neutrophil-to-Lymphocyte ratio (p = 0.001), serum urea and creatinine (p = 0.002), serum potassium (p = 0.009), C-reactive protein (p = 0.001), Lactate dehydrogenase (p = 0.005), and Ferritin (p = 0.042) of the hypoxemic patients versus non-hypoxemic group. Amongst the deceased patients, there was significant leukocytosis (p = 0.008), increased Neutrophil-to-Lymphocyte ratio (p = 0.001), elevated C-reactive protein (p = 0.001), and Lactate dehydrogenase (p = 0.009). Receiver operating characteristic curves showed Neutrophil-to-Lymphocyte ratio (p < 0.001), C-reactive protein (p < 0.001), and Lactate dehydrogenase (p < 0.001) most significantly associated with hypoxemia and death.

**Conclusion:** The inflammatory markers are a good guide for predicting the hypoxemia and disease outcome. The results concluded Neutrophil-to-Lymphocyte ratio, C-reactive protein, and Lactate dehydrogenase were effective biomarkers in predicting a severe course of COVID-19, but could not establish significant associations of serum Ferritin, Procalcitonin, and D-Dimer.

#### ARTICLE HISTORY

Received 15 August 2020  
Accepted 8 October 2020

#### KEYWORDS

COVID-19; coronavirus; biochemical markers; pandemic; mortality; infectious diseases; hypoxemia

### 1. Introduction

During the end of 2019, many cases of a mysterious pneumonia-like illness were identified in Wuhan, Hubei Province in China [1]. It was identified by the name SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) and the disease was named COVID-19 [2]. It is mainly a respiratory illness causing hypoxemia in the majority of those been infected [3]. Coronavirus family consists of single-stranded enveloped viruses and commonly causes respiratory, neurologic, hepatic, and enteric illnesses. They are divided into 4 subgroups: alpha, beta, gamma, and delta, with human infections caused mainly by the alpha and beta CoVs. Previous epidemics caused by the beta CoVs

were due to the SARS-CoV and MERS-CoV (Middle Eastern Respiratory Syndrome Coronavirus) [1].

As of now the cases caused by the virus stand at a worldwide count at 21,082,038 (757,633 deaths) and in Pakistan the total number of cases is 287,300 (6153 deaths) [4]. Despite the worldwide awareness of the infectiousness of COVID-19 and the protective measures and initiatives taken by people, it has already infected more people than SARS. This shows that SARS-CoV-2 is much more contagious [5]. The reproduction number for COVID-19 was calculated to be as high as 6.47 in this study, which is far higher than the reproduction numbers seen before in SARS and MERS [6].

The neutrophil-to-lymphocyte ratio (NLR) is a prominent predictor of disease severity in COVID-19, and levels above 9 determine poor prognosis and high mortality within patients of intensive care units [7]. Ferritin is an important acute phase reactant linked with the release of cytokines, which are responsible for the cytokine (pro-inflammatory) storm of COVID-19 [8,9]. C-reactive protein (CRP) is also an acute-phase reactant with concentrations significantly raised during sepsis as well as the pro-inflammatory process by the COVID-19 induced inflammatory cytokines [10,11]. These pro-inflammatory cytokines can ultimately lead to Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Failure (MOF) [12,13]. Procalcitonin (PCT) is widely considered to be a useful marker for bacterial sepsis, although it may be found lower in severely ill patients with viral infections [14,15]. However, COVID-19 patients with increased PCT levels were associated with 5 times greater risk of a debilitating outcome [16]. Severe sepsis patients are also associated with high levels of lactate dehydrogenase (LDH) and are a potent predictor of mortality [17]. One of the early events to occur in patients with sepsis is the activation of the coagulation cascade [18] D-dimer is a measure of the coagulation cascade, and in a way assesses the severity and the risk for the patient to develop sepsis and septic shock [19].

Based on the proinflammatory effects of all the above-mentioned markers and seeing how the main immunopathological finding of COVID-19 is the cytokine storm, we decided to investigate their roles as effective prognostic biomarkers for the disease. Several studies have shown that the prognosis, severity, and complications of COVID-19 were effectively predicted by different biomarkers [20–22]. This study aims to correlate the biochemical markers with hypoxemia and predicting the prognosis of COVID-19 patients.

## 2. Materials and methods

The study was conducted as a single centered, retrospective, observational study, and included all patients who were diagnosed as COVID-19 positive via either nasopharyngeal or oropharyngeal swab for Real-time Polymerase chain reaction. The study was carried out in a tertiary care hospital having one of the largest facility of COVID isolation units in the city having 420 beds with 3 intensive care units consisting of more than 50 beds. The data was obtained through chart reviews obtained from the hospital database having all the COVID positive patient information collectively. Out of the total 183 admitted patients, 117 were in the isolation ward, 66 were in the Intensive care unit, 148 of them recovered, while 35 deaths were reported, 89 patients were having

persisting hypoxemia (despite oxygen therapy) during the hospital stay, and the remaining 94 were non-hypoxemic with or without supplemental oxygen therapy. Hence, we divided them into two groups, those having persistent hypoxemia (defined by oxygen saturation <90%, despite supplemental oxygen therapy via nasal cannula, face mask, or high flow oxygen) and those without hypoxemia (defined by oxygen saturation  $\geq$ 90 with or without supplemental oxygen therapy). Both types of supplemental oxygen were used according to each patient's need (nasal cannula, face mask), and high flow oxygen as well in some cases. The cut-off 90% saturation was acquired by a previous study linking hypoxemia with mortality of COVID-19 patients [23].

The laboratory values of various blood markers were measured at admission within the first 24 hours of hospital stay and were compared amongst the two groups, as well as those who survived versus mortalities. The blood samples were taken immediately after admission for measuring NLR, PCT, D-dimer, Ferritin, LDH, and CRP levels. The above normal limits of laboratory values were defined as a PCT level of >0.5 ng/mL, the above-normal limit of D-dimer levels is 0.5 mcg/ml, the upper normal limit of CRP levels is 5.0 mg/L, same for LDH was 250 U/L, and for ferritin was 250 ng/ml. The neutrophil-to-lymphocyte ratio was also studied as a non-specific marker of sepsis. The upper normal range of NLR is between 3.0 and 4.0 in some studies. Any value above 9.0 may indicate severe sepsis.

The statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS version 25.0, NY, USA). All continuous variables were described by mean & standard deviation and/or median & interquartile range. The means were then compared using either independent sample t-test and/or Mann Whitney U-test, and the p-value was considered significant according to Levene statistics. Receiver operating characteristic (ROC) curves were obtained to demonstrate significant predictive outcomes of the studied biomarkers. An area under the curve (AUC) with appropriate sensitivity, specificity, positive predictive value, and negative predictive value along with a standard error was defined using cut-off obtained by applying the Youden index. A p-value of <0.05 was considered statistically significant (two-tailed). All the highly significant values of <0.001 were rounded off as 0.001. Spearman-rank correlation was used to obtain a correlation coefficient among the biochemical markers with hypoxemia.

## 3. Results

The mean age of the study population was  $52.75 \pm 16.68$  with females slightly younger than

**Table 1.** Demographic data of the study population (n = 183).

S.no #	Characteristics	Total (n = 183)	Non-Hypoxemic (n = 94)	Hypoxemic (n = 89)	p-value
1	Median age (IQR)	55.00 (39.00–66.00)	50.00 (34.75–65.00)	63.00 (57.00–69.00)	0.009 <sup>#</sup>
	Mean age (in years)	52.75 ± 16.68	49.79 ± 17.06	62.31 ± 9.63	0.001*
2	<b>Males (n = 126)</b> Median (IQR)	55.50 (44.00–67.75)	54.00 (37.25–68.50)	61.50 (53.75–70.00)	0.146 <sup>#</sup>
	Mean ± SD	54.60 ± 16.19	53.35 ± 16.24	61.83 ± 11.11	0.102*
3	<b>Females (n = 57)</b> Median (IQR)	54.00 (38.00–65.00)	40.50 (31.00–55.00)	64.50 (61.00–65.75)	0.024 <sup>#</sup>
	Mean ± SD	48.92 ± 17.32	43.75 ± 17.12	63.75 ± 2.62	0.001*
4		<b>Age groups</b>			-
	0–25	4 (2.18%)	4 (4.25%)	0 (0.0%)	0.115**
	26–50	73 (39.89%)	43 (45.74%)	30 (33.70%)	
	51–75	95 (51.91%)	44 (46.80%)	51 (57.30%)	
	>75	11 (6.01%)	3 (3.19%)	8 (8.98%)	
5		<b>Hospital stay</b>			-
	Isolation ward	117 (63.93%)	87 (74.35%)	30 (25.64%)	0.001**
	Intensive care unit (ICU)	66 (36.06%)	7 (10.60%)	59 (89.39%)	
6	Non-Hypoxemic patients (n = 94)		Hypoxemic patients (n = 89)		-
	Males: 70 (55.55%)	Females: 24 (42.10%)	Males: 56 (44.44%)	Females: 33 (57.89%)	0.373 <sup>^</sup>

<sup>^</sup> indicates Chi-square test used to compute the p-value. <sup>#</sup> indicates Mann Whitney U-test to compute the p-value. \* indicates Independent sample t-test used to compute the p-value. \*\* indicates Fisher's exact test to compute the p-value.

males. The most common age group was 50–75 years with hypoxemia found slightly more in elder age groups (p = 0.115). Females were slightly more prone to hypoxemia (p = 0.373). The majority of the patients were having mild to moderate symptoms and were admitted in isolation ward (63.93%), while the rest 36.06% having a severe disease was admitted in the Intensive care unit (ICU). The descriptive statistics of the study population are given in Table 1.

Amongst the patients with hypoxemia versus non-hypoxemic group, there were significant differences in mean hemoglobin (p = 0.028), total leukocyte count (p = 0.005), Neutrophil to Lymphocyte ratio, (p = 0.001), serum urea and creatinine (p = 0.002), serum potassium (p = 0.009), CRP levels (p = 0.001), LDH (p = 0.005), and Ferritin (p = 0.042). Amongst the deceased patients, there was significant leukocytosis (p = 0.008), increased NLR (p = 0.001), elevated CRP level (p = 0.001), and LDH (p = 0.001), as shown in Table 2.

The spearman's correlation of hypoxemia with biochemical markers showed NLR (r = 0.485, p < 0.001), LDH (r = 0.488, p < 0.001), CRP (r = 0.422, p < 0.001), and Ferritin (r = 0.349, p = 0.004) significantly correlating while PCT (r = 0.103, p = 0.550), and D-dimer (r = 0.465, p = 0.093) found not significantly correlating.

ROC curves for hypoxemia showed NLR (AUC: 0.828, p < 0.001), CRP (AUC: 0.775, p < 0.001), LDH (AUC: 0.836, p < 0.001), Ferritin (AUC: 0.678, p = 0.039), Procalcitonin (AUC: 0.667, p = 0.056), and D-dimer (AUC: 0.771, p = 0.093), while ROC curves for deceased patients showed NLR (AUC: 0.858, p < 0.001), CRP (AUC: 0.764, p = 0.001), LDH (AUC: 0.844, p = 0.001), Ferritin (AUC: 0.661, p = 0.131), Procalcitonin (AUC: 0.723, p = 0.180), and D-dimer (AUC: 0.772, p = 0.148), as shown in Table 3 and Figures 1 & 2.

#### 4. Discussion

The recent pandemic of COVID-19 has prompted risk stratification of disease severity that could aid clinical management. One study concluded that CRP was elevated in 60.7% of the COVID-19 patients [24]. A significant association of increased CRP and hypoxemia was also studied with mean values higher as compared to our results [25]. Various studies reached the same conclusion in there about the use of CRP to predict disease prognosis with higher mean values reported [15,26,27]. One such study also linked CRP with the need for mechanical ventilation. It concluded an AUC of 0.830 with maximal cut-off 97.0 mg/L predicting the need for mechanical ventilation, compared to our hypoxemia cut-off 99.30 mg/L with an AUC of 0.775 at 77% sensitivity and 85% positive predictive value [28]. Another study gave an AUC of 0.714 at cut-off 20.3 mg/L for disease severity [7], while we report an AUC of 0.764 at cut-off 135.90 mg/L for death. Gao et al. has reported a lower AUC (0.600) as compared to ours [26].

NLR is another important marker of sepsis studied by various studies, one of them predicting disease severity at an optimal cut-off 3.3, AUC of 0.841 at a sensitivity of 88% and specificity of 63% [7]. While we report an AUC of 0.828 at 74% sensitivity, 88% specificity, and 85% Positive predictive value for hypoxemia at cut-off 4.39, and AUC of 0.858 with 75% sensitivity, 76% specificity, and 92% positive predictive value for death at cut-off 5.67. Hence, both CRP and NLR have PPV > 90% for predicting mortality at above normal limit measured values. Few studies demonstrated LDH to also be significantly raised in patients with disease severity however, levels were much lower as compared to our reported findings [29,30]. The significance of ferritin to predict the disease severity has been reported by many studies [25,30,31]. A study analyzing the severity of hypoxemic respiratory

**Table 2.** Comparison of initial laboratory investigations (means) amongst the patients of COVID-19 (n = 183).

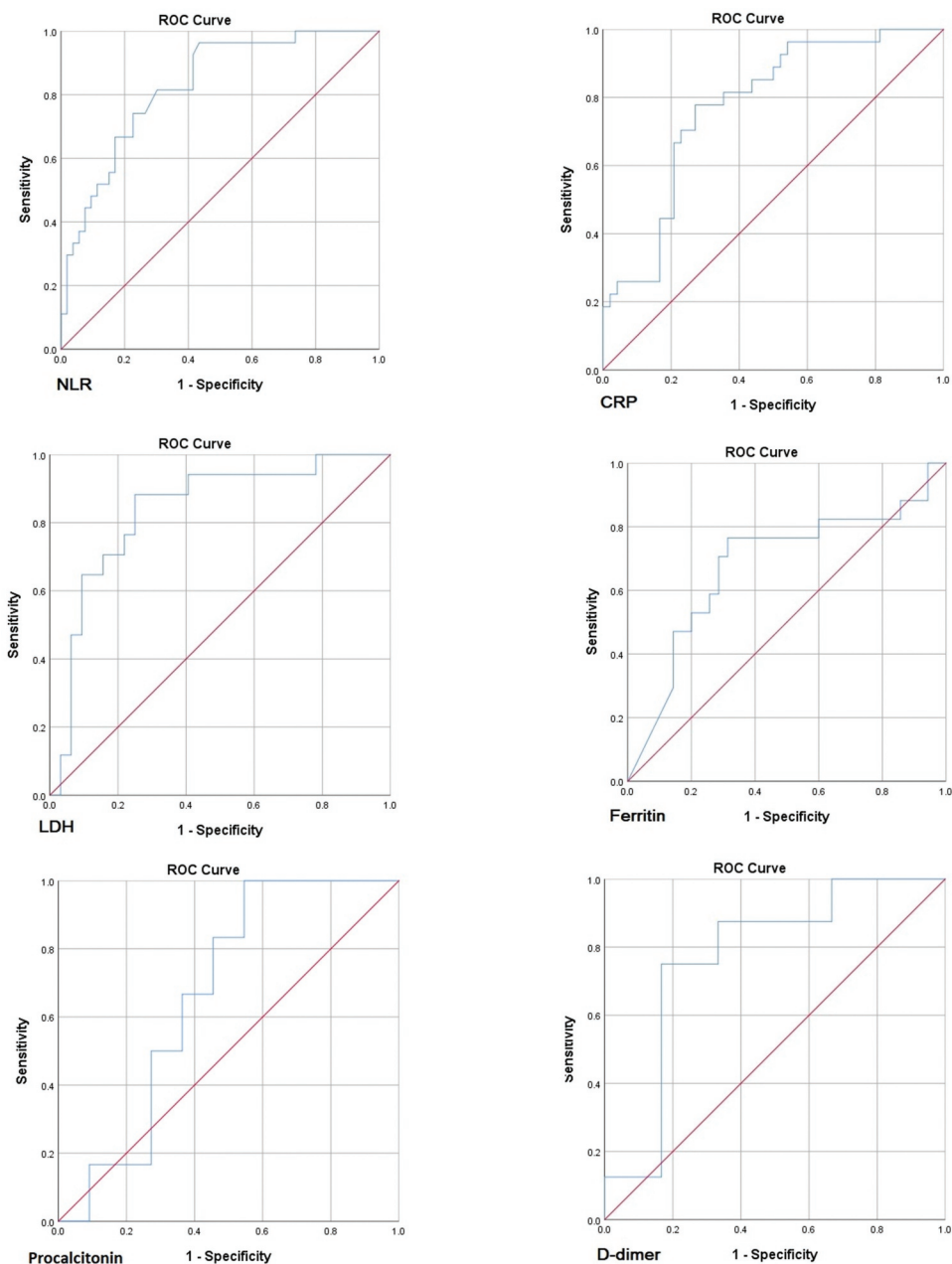
#	Laboratory investigation	Non-Hypoxic (n = 94) Mean ± standard deviation	Hypoxic (n = 89) Mean ± standard deviation	p-value	Survived (n = 148) Mean ± standard deviation	Death (n = 35) Mean ± standard deviation	p-value
1	Hemoglobin	13.20 ± 2.33	12.00 ± 2.07	0.028*	12.69 ± 2.33	12.55 ± 2.05	0.826
2	MCV	83.07 ± 7.65	80.36 ± 8.57	0.163	82.68 ± 7.54	79.18 ± 9.71	0.139
3	Platelets	235.20 ± 75.92	270.46 ± 131.15	0.132	243.35 ± 88.84	279.62 ± 124.27	0.202
4	TLC	8.08 ± 4.07	13.67 ± 9.04	0.005*	8.41 ± 4.24	15.00 ± 9.42	0.015*
5	Neutrophil to lymphocyte ratio (NLR)	4.09 ± 4.16	11.64 ± 10.47	0.001*	4.00 ± 3.70	14.12 ± 11.76	0.004*
6	Urea	30.06 ± 22.93	60.09 ± 40.21	0.001*	33.36 ± 28.69	63.30 ± 42.85	0.017*
7	Creatinine	0.90 ± 0.29	1.57 ± 0.98	0.002*	1.01 ± 0.70	1.52 ± 0.65	0.013*
8	Sodium	137.12 ± 4.28	137.50 ± 4.66	0.719	137.66 ± 3.71	135.93 ± 5.73	0.157
9	Potassium	4.17 ± 0.61	4.65 ± 0.79	0.009*	4.25 ± 0.63	4.55 ± 0.81	0.124
10	Chloride	102.59 ± 3.90	101.07 ± 6.82	0.202	103.05 ± 3.97	99.56 ± 7.30	0.083
11	Bicarbonate	19.42 ± 3.26	17.50 ± 4.42	0.055	19.62 ± 3.17	17.37 ± 5.07	0.109
12	CRP	77.60 ± 88.77	167.62 ± 100.72	0.001*	83.28 ± 94.00	177.73 ± 89.60	0.001*
13	LDH	448.50 ± 348.60	782.00 ± 362.93	0.005*	441.46 ± 334.83	889.56 ± 389.20	0.009*
14	Ferritin	496.91 ± 652.44	1003.89 ± 836.04	0.042*	514.96 ± 661.76	937.90 ± 811.28	0.111
15	D-dimer	1.49 ± 2.13	3.45 ± 2.76	0.175	2.58 ± 3.54	4.32 ± 1.89	0.169
16	Troponin I	114.00 ± 77.75	196.52 ± 165.91	0.131	121.57 ± 130.56	207.88 ± 161.61	0.189
17	Pro-BNP	939.30 ± 6555.28	1240.50 ± 1698.05	0.162	1119.46 ± 6370.15	2161.53 ± 1319.64	0.270
18	Procalcitonin	0.38 ± 0.54	4.70 ± 17.25	0.675	0.84 ± 1.19	10.60 ± 27.20	0.246
19	ESR	70.40 ± 127.20	80.84 ± 111.19	0.895	83.33 ± 38.27	63.00 ± 60.81	0.668

All P-values calculated by independent sample t-test (\* indicates significant values of < 0.05).

**Table 3.** ROC statistics of the COVID-19 patients for Hypoxemia and deaths.

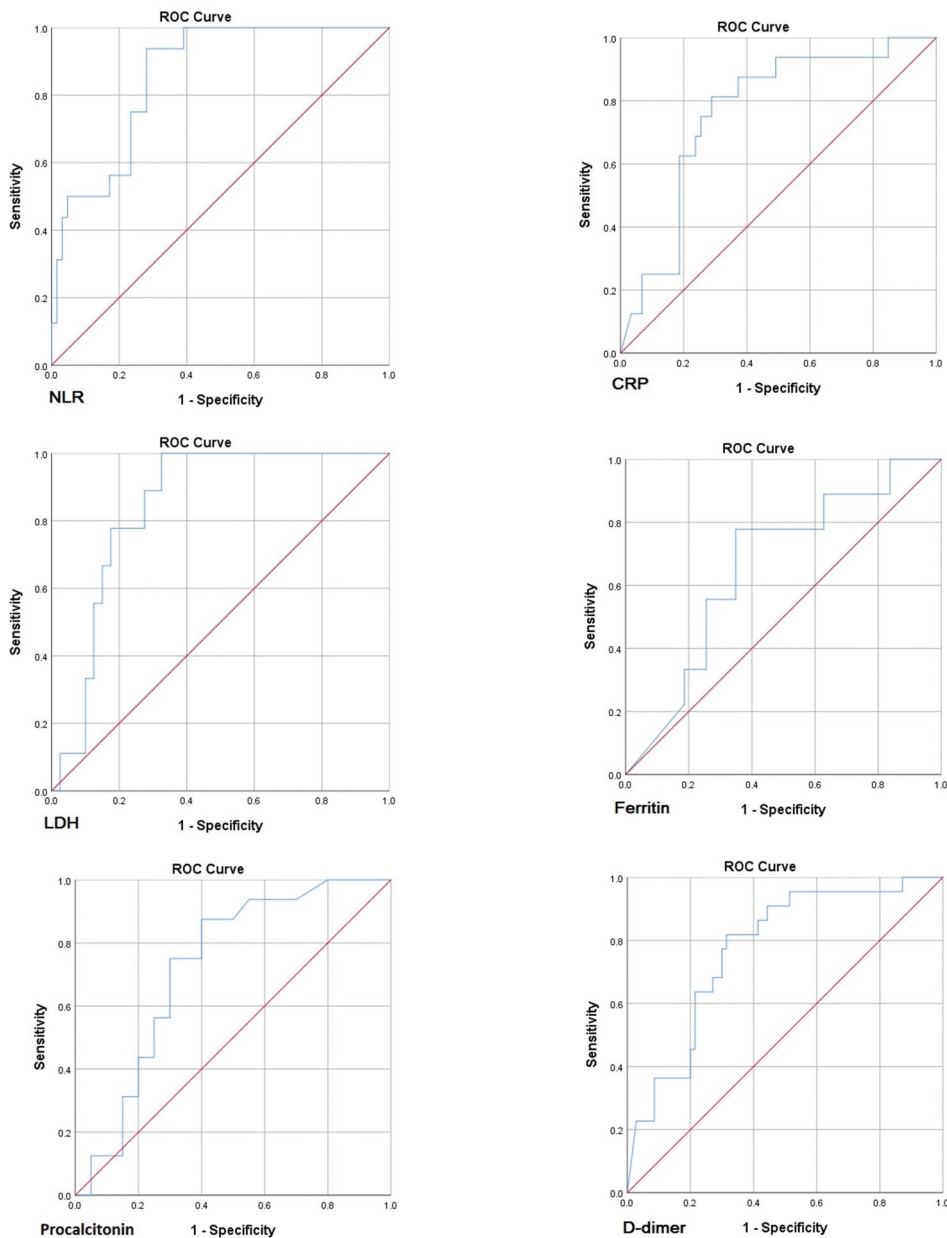
Variable state	AUC	S.E	95% confidence interval	Sensitivity	Specificity	PPV	NPV	p-value
1			<b>NLR</b>					
<b>Hypoxemia</b> (cut off: 4.39)	<b>0.828</b>	0.046	0.738–0.919	<b>74.1%</b>	<b>77.4%</b>	85.4%	62.5%	<0.001
<b>Death</b> (cut off: 5.67)	<b>0.858</b>	0.044	0.773–0.944	<b>75.0%</b>	<b>76.6%</b>	92.5%	44.4%	<0.001
2			<b>CRP (mg/L)</b>					
<b>Hypoxemia</b> (cut off: 99.30)	<b>0.775</b>	0.054	0.668–0.881	<b>77.8%</b>	<b>72.9%</b>	85.4%	61.8%	<0.001
<b>Death</b> (cut off: 135.90)	<b>0.764</b>	0.063	0.641–0.887	<b>75.0%</b>	<b>74.6%</b>	91.7%	44.4%	0.001
3			<b>LDH (U/L)</b>					
<b>Hypoxemia</b> (cutoff: 527.53)	<b>0.836</b>	0.062	0.715–0.957	<b>82.4%</b>	<b>75.0%</b>	88.9%	63.6%	<0.001
<b>Death</b> (cutoff: 655.00)	<b>0.844</b>	0.055	0.736–0.953	<b>77.8%</b>	<b>82.5%</b>	94.3%	50.0%	0.001
4			<b>Ferritin (ng/ml)</b>					
<b>Hypoxemia</b> (cut off: 338.28)	<b>0.678</b>	0.086	0.510–0.846	<b>76.5%</b>	<b>68.6%</b>	85.7%	54.2%	0.039
<b>Death</b> (cut off: 389.46)	<b>0.661</b>	0.093	0.480–0.843	<b>77.8%</b>	<b>65.1%</b>	93.3%	31.8%	0.131
5			<b>Procalcitonin (ng/ml)</b>					
<b>Hypoxemia</b> (cutoff: 0.075)	<b>0.667</b>	0.163	0.484–0.837	<b>75.0%</b>	<b>66.7%</b>	28.6%	93.8%	0.056
<b>Death</b> (cutoff: 0.085)	<b>0.723</b>	0.124	0.525–0.906	<b>81.8%</b>	<b>50.0%</b>	75.0%	60.0%	0.180
6			<b>D-Dimer (mcg/ml)</b>					
<b>Hypoxemia</b> (cutoff: 0.84)	<b>0.771</b>	0.143	0.490–0.942	<b>87.5%</b>	<b>66.7%</b>	80.0%	77.8%	0.093
<b>Death</b> (cutoff: 0.96)	<b>0.772</b>	0.168	0.471–0.869	<b>85.7%</b>	<b>42.9%</b>	75.0%	60.0%	0.148

PPV: Positive predictive value, NPV: negative predictive value, CRP: C-reactive protein, AUC: area under curve, S.E: standard error of mean, ROC: receiver operating characteristic, LDH: lactate dehydrogenase, NLR: neutrophil-to-lymphocyte ratio.



**Figure 1.** Receiver operating characteristic curves of studied biochemical markers for Hypoxemia.





**Figure 2.** Receiver operating characteristic curves of studied biochemical markers for Death.

failure in COVID-19 patients noted that serum ferritin was insignificant among the groups [32]. Rather, serum iron was correlating with disease severity and hypoxemia. The levels of ferritin were much higher in this study in the non-severe group contrasting our results but the association between the levels of ferritin and disease severity was also found statistically insignificant in our study [32].

Our results did not demonstrate procalcitonin (PCT) to be significantly associated with hypoxemia, similar to another study previously reported the insignificance of PCT as an effective biomarker [26]. On the contrary, several studies have reported a significant association between the elevated levels of PCT and disease severity and mortality [27,33]. D-dimer is also associated with a severe course of coronavirus disease [22,34]. Interestingly our results did not show a significant association of d-dimer with

hypoxemia similar to some other studies [30,35]. Most of the studies conducted to predict the severity of COVID-19 have found a strong association of D-Dimer [27,28]. Our study based on its findings could not reach that conclusion. On the contrary, Gao et al. reported an AUC of 0.750 with 86% sensitivity and 82% specificity [26], compared to our AUC of 0.771 with a sensitivity of 87% and specificity of 66%. While Herold et al. have associated mechanical ventilation most accurately with CRP (AUC: 0.860) followed by LDH, PCT, and ferritin [28]. Although, D-dimer was an effective predictor of mortality in COVID-19 specified by various studies [36,37]. Overall, mortality predictions have been mostly associated in the literature with LDH, followed by CRP, D-dimer, moderately associated with NLR and PCT, and least associated with serum ferritin [38,39].

There were a few limitations of our study, we did not utilize the measurement of oxygen saturation of arterial blood gases as a partial oxygen pressure (arterial PaO<sub>2</sub>) but instead as pulse oximetry. PaO<sub>2</sub> should be cautiously interpreted as measured by pulse oximetry [38]. Estimated CO-oximeter oxygen saturation (SpO<sub>2</sub>) may be roughly  $\pm 4\%$  distinct from recorded arterial oxygen saturation. The validation of findings using calculated arterial oxygen saturation may also be a stronger criterion. Furthermore, to be able to accurately determine the lung potential for gas exchange, it is important to know the fraction of inspired oxygen (FiO<sub>2</sub>), which was not utilized in our study [40]. We solely relied on measurements by pulse oximeter to determine hypoxemia. Lastly, the biomarkers were evaluated in hospitalized patients and thus results cannot be generalizable to patients with milder COVID-19 disease who do not require hospitalization.

## 5. Conclusions

We studied the effect of various biomarkers on the hypoxemia and prognosis of COVID-19. Our findings can help in the treatment, effective management, and risk stratifying strategies of COVID-19 patients. The results from our study concluded that NLR, CRP, and LDH were effective biomarkers in predicting a severe course of COVID-19 hypoxemia and mortality, but we could not establish significant associations of PCT, serum Ferritin and D-Dimer in predicting the severity of COVID-19 associated hypoxemia and mortality.

## Disclosure statement

The authors declare no conflicts of interest with this article's content.

## Funding

This work is not supported by any sponsors. No funding required in this study.

## Ethical approval statement

Ethical approval was taken in this study from the institutional review board, and consent to participate has been taken from all the patient's guardians with informed written consent.

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