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Predictive value of hematologic indices in COVID-19 disease outcomes

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Abstract

Introduction: COVID-19 was declared a worldwide concern for public health in January 2020 by the World Health Organization. Most patients manifest mild symptoms. In more severe cases it can lead to sepsis, acute respiratory distress syndrome and other organ dysfunction. Lymphopenia, increased inflammatory markers and dysregulated liver enzymes are observed in many patients and is related to higher mortality rates. **Materials and Methods:** We evaluated two hundred and sixty-eight patients in this study. All patients had dyspnea, and O2 saturation below 93% and were tested positive for COVID-19 through RT-PCR. Patients' demographic, clinical and paraclinical information were obtained on admission and disease outcomes were assessed based on these data. The evaluated indices were previously shown to be altered in patients with different disease outcomes. **Results:** From a total of 268 included patients, 40% had severe disease, 29% were admitted to ICU, 22% required mechanical ventilation and 24% died during hospitalization. WBC counts, neutrophil counts, NLR, serum LDH activity and serum albumin levels were the most powerful factors in predicting disease outcomes. **Conclusion:** COVID-19 disease severity and outcomes were affected by hematologic indices and laboratory results.

Keywords: COVID-19, Neutrophil, White blood cell, Neutrophil lymphocyte ratio

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Introduction

COVID-19 was first seen in December 2019 in Wuhan, China and was declared a worldwide concern for public health in January 2020 by World Health Organization (1). The disease was named "COVID-19" in February 2020 and the virus was named as "SARS-CoV-2" (2). SARS-CoV-2 was the third coronavirus in the past 20 years that can infect human species (3). About 81% of the patients manifest mild symptoms, the symptoms can be severe in 14% of the patients and it can lead to sepsis, acute respiratory distress syndrome and other organs' failure in 5% of the patients (4).

Previous studies have shown lung involvement in CT-scan in most patients. Lymphopenia, increased inflammatory markers (like ferritin and C-reactive protein) and elevated AST and ALT levels are also observed in many patients (5, 6). It is shown that lymphopenia presents despite normal white blood cell count and lymphocyte count is related with disease severity and prognosis (7). Higher mortality rates are observed among patients with lymphopenia, thrombocytopenia, elevated inflammatory markers (like CRP, LDH and ferritin) and coagulopathies (8, 9).

As mentioned, these hematologic indices and inflammatory markers are shown to have a predictive role in determining the disease outcome. In this study we evaluated this predictive role in COVID-19 patients.

Materials and methods

Two hundred and sixty-eight patients were enrolled in this study. All patients were admitted to Razi Hospital, Rasht from March 2021 until March 2022. All patients had dyspnea, O_2 saturation below 93% and were tested positive for COVID-19 through RT-PCR. Patients with underlying medical condition (which is known to affect blood cell counts or other evaluated lab data e.g. hematologic malignancies) were excluded from this study. Demographic and clinical information were gathered from patients' admission records. A blood test was administered in admission to evaluate hematologic and inflammatory indices.

Disease severity was classified as moderate ($90 < SPO_2 < 94$ or less than 50% lung involvement in CT-Scan) and severe ($SPO_2 < 90$ or respiratory rate over 30 or $PCO_2/FIO_2 < 300$). The patients were also classified by admission to intensive care unit, death within hospital admission and requiring ventilation. Patients' demographic data, past medical records, inflammatory and hematologic indices in admission and clinical presentation were assessed based on the mentioned categories.

In this survey, quantitative data are shown as "mean (standard deviation)" and qualitative data are shown as "frequency (percentile)". Man-Whitney test was done to compare the hematologic indices based on disease severity (moderate or severe), ICU admission (yes or no), death within hospital admission (yes or no) and requiring mechanical ventilation (yes or no). Area under the receiver operating characteristics curve (AUC for ROC curve) was shown to evaluate the potential of hematologic indices to predict disease severity, ICU admission, death within hospital admission and requirement of mechanical ventilation. All results were analyzed with a 95% confidence interval.

Results

Two hundred and sixty-eight patients, who were admitted to Razi hospital with a definite diagnosis of COVID-19, were enrolled in this study. 109 patients (41%) were male and the mean age was 56 ± 16.6. 105 patients (39%) had hypertension, 75 patients (28%) had diabetes mellitus,30 patients (11%) and ischemic heart disease, eleven patients (4%) had an underlying pulmonary disease and ten patients (4%) had chronic kidney disease. The mean systolic blood pressure in admission was 123.2 ± 19.4, the mean pulse rate and respiratory rate were 90.1 ±12.8 and 23.2 ±4.4 and the mean O2 saturation was 89.9 ± 8.3. All clinical and demographic data are shown in table 1.

Lab test results in admission are also shown in table 2. As shown in table 3, 108 patients (40%) had severe disease, 78 patients (29%) were admitted in ICU, 58 patients (22%) required mechanical ventilation and 63 patients (24%) died during hospitalization.

Table 1. Patients' clinical and demographic data.

		Frequency (percentage) or mean ± standard deviation
Age (years)		56 ± 16.6
Gender	Male	109 (41%)
	Female	159 (59%)
HTN		105 (39%)
DM		75 (28%)
CKD		10 (4%)
Pulmonary disease		11 (4%)
IHD		30 (11%)
Temperature		37.1 ± 0.5
Systolic blood pressure		123.2 ± 19.4
Diastolic blood pressure		76.1 ± 12.7
Pulse rate		90.1 ± 12.8
Respiratory rate		23.2 ± 4.4
O_2 saturation		89.9 ± 8.3

Table 2. Patients' lab test results in admission.

	Mean ± SD	Median (IQR)
WBC (× 10^6/mL)	8.1 ± 4.3	7.1 (5.1 – 10)
Hb (g/dL)	12 ± 1.9	12.2 (10.8 – 13.2)
RDW (%)	14 ± 2	13.5 (12.7 – 14.8)
MCV (fL)	84 ± 7.9	85 (80.5 – 88.4)
Platelets (10^6/mL)	220.5 ± 97.1	203 (152 – 263.5)
Neutrophils (10^6/mL)	6.61 ± 3.8	5.7 (4 – 8.5)
Lymphocytes (10^6/mL)	1.1 ± 0.9	0.8 (0.6 – 1.3)
Monocytes (10^6/mL)	0.4 ± 0.3	0.3 (0.2 – 0.5)
NLR	8.2 ± 6	6.8 (4 – 10.7)
PLR	288.5 ± 206	228.5 (158.8 – 356.6)
MLR	0.5 ± 0.4	0.3 (0.2 – 0.6)
PT (s)	12.7 ± 1.1	12 (12 – 12.7)
PTT (s)	34.6 ± 0.9	32 (30 – 37)
BS (mg/dL)	157.7 ± 82.3	133.5 (110.1 – 170)
BUN (mg/dL)	22.2 ± 18.6	16 (11.3 – 23)
Cr (mg/dL)	1.24 ± 1	1 (0.8 – 1.2)
AST (U/L)	54.8 ± 44.2	44 (31 – 65)
ALT (U/L)	43.8 ± 46.6	29 (21 – 45.8)
ALP (U/L)	198 ± 85	178 (145.3 – 230)
LDH (U/L)	904 ± 372.9	841 (654 – 1078.8)
Alb (g/dL)	3.6 ± 0.5	3.6 (3.5 – 3.9)
ESR (mm/h)	54.6 ± 22.9	55 (39 – 66)
pH	7.37 ± 0.07	7.38 (7.34 – 7.41)
PCO_2 (mmHg)	42.1 ± 8.3	41.8 (36.8 – 45.7)
HCO_3 (mmol/L)	25.1 ± 4.1	25.1 (22.4 – 27.9)

Table 3. Rates of disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.

		Frequency (Percent)
Disease severity	Moderate	160 (60%)
	Severe	108 (40%)
ICU admission	No	190 (71%)
	Yes	78 (29%)
Mechanical ventilation	Not required	210 (78%)
	Required	58 (22%)
Death during hospitalization	No	205 (76%)
	Yes	63 (24%)

Table 4 & 5 show the comparison of lab test results based on disease severity, ICU admission, mechanical ventilation and death during hospitalization. White blood cells, neutrophil count, neutrophil to lymphocyte ratio, prothrombin time, random plasma glucose, blood urea nitrogen, AST, LDH and erythrocyte sedimentation rate were significantly higher in patients who had severe disease, required mechanical ventilation, were admitted to ICU or died during hospitalization.

Table 4. Comparison of lab test results between groups of disease severity and ICU admission.

	Disease severity		P value	ICU admission		P value
	Moderate	Severe		No	Yes	
WBC (× 10^6/mL)	6.7 (4.7 – 9.9)	7.9 (5.5 – 10.6)	**0.010**	6.7 (4.9 – 9.4)	8.7 (5.6 – 12.2)	**0.001**
Hb (g/dL)	12 (10.7 – 13.1)	12.4 (10.9 – 13.4)	0.139	12.1 (10.9 – 13.1)	12.4 (10.7 – 13.4)	0.400
RDW (%)	13.3 (12.5 – 15)	13.9 (12.8 – 14.7)	0.338	13.3 (12.6 – 14.8)	14.1 (12.9 – 14.6)	0.096
MCV (fL)	86.2 (82 – 89)	83.4 (79.1 – 86.9)	**0.003**	86.2 (82.2 – 89.5)	82.1 (78.5 – 85.8)	< **0.001**

Platelets (10^6/mL)	194 (146 – 257.8)	213 (169.3 – 283)	0.068	203 (147.8 – 262)	201.5 (157.5 – 271.5)	0.703
Neutrophils (10^6/mL)	5.3 (3.5 – 7.6)	6.4 (4.5 – 9)	**0.002**	5.3 (3.6 – 7.5)	7.4 (4.8 – 10.3)	**< 0.001**
Lymphocytes (10^6/mL)	0.9 (0.6 – 1.4)	0.8 (0.6 – 1.1)	0.239	0.9 (0.6 – 1.4)	0.8 (0.6 – 1.1)	0.170
Monocytes (10^6/mL)	0.3 (0.2 – 0.5)	0.3 (0.2 – 0.5)	0.962	0.3 (0.2 – 0.5)	0.3 (0.2 – 0.5)	0.516
NLR	5.5 (3.8 – 8.8)	8.6 (4.7 – 11.3)	**0.001**	5.4 (3.8 – 8.8)	8.8 (5.1 – 14.5)	**< 0.001**
PLR	208.3 (148.3 – 319.9)	272.9 (167.8 – 376.7)	**0.010**	220.2 (151.1 – 339.6)	268.1 (160 – 384.3)	0.118
MLR	0.3 (0.2 – 0.6)	0.4 (0.2 – 0.6)	0.656	0.3 (0.2 – 0.6)	0.4 (0.2 – 0.6)	0.931
PT (s)	12 (12 – 12.7)	12.7 (12 – 13.4)	**< 0.001**	12 (12 – 12.7)	12.7 (12 – 13.4)	**< 0.001**
PTT (s)	31 (30 – 36)	33 (30 – 39)	**0.036**	31 (30 – 36)	33 (30 – 40)	**0.007**
BS (mg/dL)	129 (110 – 155.8)	139.5 (110.3 – 202.8)	**0.025**	129 (107.8 – 155.3)	150 (115.8 – 219.3)	**0.003**
BUN (mg/dL)	16 (11 – 21.8)	18 (12 – 25.8)	**0.025**	16 (11 – 21.3)	19 (12 – 26.8)	**0.017**
Cr (mg/dL)	1 (0.9 – 1.2)	1 (0.8 – 1.3)	0.958	1 (0.89 – 1.2)	1 (0.8 – 1.33)	0.330
AST (U/L)	38 (27.3 – 52)	50.5 (38 – 73.5)	**< 0.001**	39 (29 – 54)	52.5 (41 – 86.8)	**< 0.001**
ALT (U/L)	28 (21 – 45)	31.5 (22 – 49.3)	0.257	28 (21 – 44)	36 (23 – 56.3)	**0.036**
ALP (U/L)	185 (151 – 232.8)	170 (144.3 – 221)	0.180	177.5 (146 – 225)	184 (145 – 240.5)	0.489
LDH (U/L)	731.5 (580 – 938.5)	1007.5 (786 – 1305)	**< 0.001**	741.5 (607.5 – 950.5)	1070 (796 – 1390)	**< 0.001**
Alb (g/dL)	3.7 (3.4 – 4)	3.4 (3.2 – 3.8)	**< 0.001**	3.7 (3.4 – 4)	3.4 (3.2 – 3.8)	**< 0.001**
ESR (mm/h)	53.5 (35.3 – 63)	58 (40.5 – 75)	**0.020**	54.5 (39.8 – 65)	60 (37.8 – 78.5)	0.140
pH	7.39 (7.35 – 7.41)	7.37 (7.33 – 7.41)	0.245	7.39 (7.35 – 7.42)	7.36 (7.33 – 7.4)	**0.001**
PCO_2 (mmHg)	42.7 (38.9 – 46.2)	40.1 (35.3 – 45)	**0.011**	42.3 (38.2 – 46.2)	40.1 (35.1 – 44.2)	**0.014**
HCO_3 (mmol/L)	26 (23.5 – 28.2)	24.1 (21.5 – 27.3)	**0.002**	26 (23.5 – 28.3)	23.7 (20 – 26.2)	**< 0.001**

Table 5. Comparison of lab test results between groups of mechanical ventilation and death during hospitalization.

	Mechanical ventilation			Death during hospitalization		
	Not required	Required	**P value**	No	Yes	**P value**
WBC (× 10^6/mL)	6.7 (4.8 – 9.5)	9.15 (6.5 – 13.1)	**< 0.001**	6.7 (4.8 – 9.5)	8.7 (5.8 – 13)	**0.001**
Hb (g/dL)	12.2 (10.9 – 13.1)	12.15 (10.9 – 13.5)	0.547	12.2 (10.9 – 13.1)	12 (10.7 – 13.4)	0.968
RDW (%)	13.4 (12.6 – 14.8)	14 (12.8 – 14.7)	0.545	13.3 (12.6 – 14.7)	14.2 (12.9 – 14.8)	0.101
MCV (fL)	85.2 (81.4 – 89)	82.9 (78.3 - 87)	**0.008**	85.3 (81.5 – 89)	82.8 (77.9 – 87)	**0.002**
Platelets (10^6/mL)	201.5 (149.5 – 261.3)	206.5 (164 - 281)	0.400	204 (152 – 262)	197 (154 – 271)	0.813
Neutrophils (10^6/mL)	5.3 (3.6 – 7.8)	7.9 (5 – 10.5)	**< 0.001**	5.3 (3.6 – 7.9)	7.1 (4.9 – 10.1)	**< 0.001**
Lymphocytes (10^6/mL)	0.9 (0.6 – 1.3)	0.9 (0.7 – 1.1)	0.719	0.9 (0.6 – 1.4)	0.8 (0.6 – 1.1)	0.677
Monocytes (10^6/mL)	0.3 (0.2 – 0.5)	0.3 (0.2 – 0.5)	0.378	0.3 (0.2 – 0.5)	0.3 (0.2 – 0.5)	0.592
NLR	5.7 (3.9 – 9.8)	8.7 (5.1 – 12.7)	**0.002**	5.7 (3.9 – 9.6)	8.7 (5.1 – 11.4)	**0.001**
PLR	226.6 (159.1 – 359.8)	232.7 (156 - 350)	0.845	226.1 (159 – 354.8)	234.2 (157.2 – 364.1)	0.787
MLR	0.3 (0.2 – 0.6)	0.4 (0.2 – 0.6)	0.980	0.3 (0.2 – 0.6)	0.4 (0.2 – 0.6)	0.706

PT (s)	12 (12 – 12.7)	12.7 (12 – 13.4)	< **0.001**	12 (12 – 12.7)	12.7 (12 – 13.4)	< **0.001**
PTT (s)	32 (30 - 37)	33 (30 – 40)	0.073	32 (30 – 36)	35 (30 – 40)	**0.005**
BS (mg/dL)	128.5 (106 - 156)	153 (120.8 – 229.3)	< **0.001**	130 (107.5 – 156)	150 (117 – 216)	**0.004**
BUN (mg/dL)	16 (11 - 22)	20 (13.8 – 40.8)	**0.001**	16 (11 – 22)	19 (12 – 48)	**0.003**
Cr (mg/dL)	0.97 (0.84 – 1.18)	1.1 (0.88 – 1.64)	**0.036**	0.96 (0.84 – 1.17)	1.1 (0.9 – 1.68)	**0.018**
AST (U/L)	42 (30 - 55)	53 (42.5 – 90.5)	< **0.001**	41 (29 – 54)	54 (44 – 90)	< **0.001**
ALT (U/L)	28 (21 – 46.8)	33.5 (22.5 – 45.5)	0.402	28 (21 – 45.5)	34 (23 – 47)	0.342
ALP (U/L)	177.5 (145 – 225.5)	184 (148.3 – 124.5)	0.365	178 (147.5 – 232)	178 (145 – 224)	0.915
LDH (U/L)	788 (623 - 989)	1084.5 (779.8 – 1412.5)	< **0.001**	775 (611 – 974.5)	1085 (786 – 1400)	< **0.001**
Alb (g/dL)	3.7 (3.4 – 3.9)	3.4 (3.2 – 3.8)	**0.001**	3.7 (3.4 – 3.9)	3.4 (3.2 – 3.8)	**0.001**
ESR (mm/h)	54 (38 – 64.3)	60 (42 – 50.5)	**0.008**	54 (38 – 64.5)	60 (42 – 80)	**0.016**
pH	7.39 (7.35 – 7.42)	7.35 (7.32 – 7.39)	**0.001**	7.39 (7.35 – 7.42)	7.35 (7.31 – 7.40)	< **0.001**
PCO_2 (mmHg)	42.2 (38.2 – 46.2)	39.2 (34.5 – 44.4)	**0.015**	42.2 (38.4 – 46.1)	38.8 (34.3 – 44.6)	**0.008**
HCO_3 (mmol/L)	25.6 (23.4 – 28.2)	23 (20 – 26.1)	**<0.001**	25.6 (23.5 – 28.2)	22.7 (19 – 26.3)	< **0.001**

On the other hand, mean corpuscular volume, serum albumin levels, blood pH, pCO2, HCO3 and base excess were significantly lower in the patients with mentioned outcomes. Comparison of WBC count, Neutrophil count and NLR is also shown in figure 1-3.

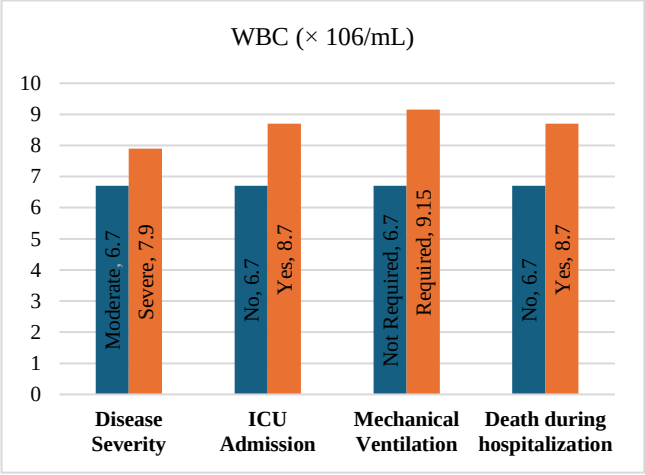


Figure 1. Comparison of WBC count between different groups of disease outcome.

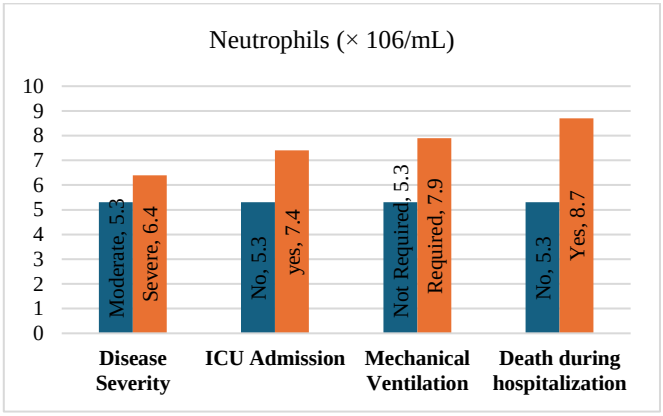


Figure 2. Comparison of Neutrophil count between different groups of disease outcome.

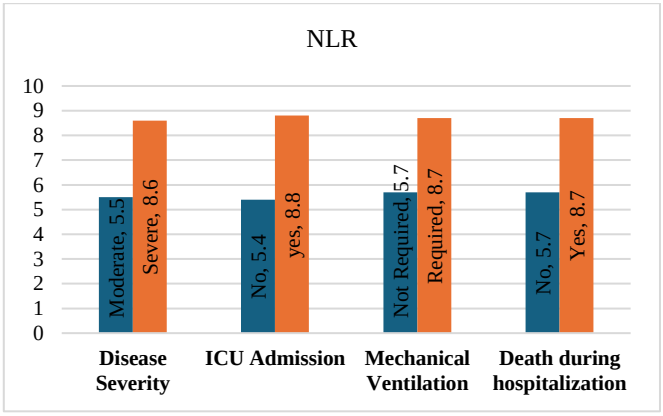


Figure 3. Comparison of NLR between different groups of disease outcome.

We used AUC of ROC curve to determine the predicting effect of lab results on the disease severity and outcomes. Table 6 and figure 4 – 8 show the predicting potential of laboratory results about disease severity, ICU admission, mechanical ventilation and death during hospitalization. LDH, AST and serum albumin levels were the most powerful predicting factors for disease severity. LDH, NLR and HCO3 were the most significant predicting factors for ICU admission. LDH, neutrophil count and WBC count were potentially the best predictors for mechanical ventilation. Death during hospitalization was predicted by LDH, HCO3 and AST better than other laboratory results.

Table 6. Effect of different factors on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.

	Severity		**ICU admission**		**Intubations**		**In-hospital mortality**	
	AUC (95% CI)	P value	AUC (95% CI)	P value	AUC (95% CI)	P value	AUC (95% CI)	P value
WBC (× 10^6/mL)	0.593 (0.524 – 0.662)	**0.010**	0.636 (0.558 – 0.715)	**0.001**	0.624 (0.548 – 0.701)	**0.001**	0.672 (0.593 – 0.750)	**<0.001**
Hb (g/dL)	0.000 (0.000 – 0.000)	0.139	0.000 (0.000 – 0.000)	0.968	0.000 (0.000 – 0.000)	0.400	0.000 (0.000 – 0.000)	0.547
RDW (%)	0.535 (0.465 – 0.604)	0.338	0.568 (0.491 – 0.646)	0.101	0.565 (0.493 – 0.636)	0.096	0.526 (0.446 – 0.606)	0.545
MCV (fL)	0.608 (0.539 – 0.677)	**0.003**	0.629 (0.551 – 0.708)	**0.002**	0.678 (0.611 – 0.745)	**<0.001**	0.614 (0.534 – 0.695)	**0.008**
Platelets (× 10^6/mL)	0.000 (0.000 – 0.000)	0.068	0.000 (0.000 – 0.000)	0.813	0.000 (0.000 – 0.000)	0.703	0.000 (0.000 – 0.000)	0.400
Neutrophils (× 10^6/mL)	0.612 (0.544 – 0.679)	**0.002**	0.657 (0.581 – 0.733)	**<0.001**	0.654 (0.580 – 0.727)	**<0.001**	0.687 (0.611 – 0.763)	**<0.001**
Lymphocytes (× 10^6/mL)	0.000 (0.000 – 0.000)	0.239	0.000 (0.000 – 0.000)	0.677	0.000 (0.000 – 0.000)	0.170	0.000 (0.000 – 0.000)	0.719
Monocytes (× 10^6/mL)	0.000 (0.000 – 0.000)	0.962	0.000 (0.000 – 0.000)	0.592	0.000 (0.000 – 0.000)	0.516	0.000 (0.000 – 0.000)	0.378
NLR	0.625 (0.556 – 0.693)	**<0.001**	0.645 (0.570 – 0.720)	**<0.001**	0.675 (0.603 – 0.747)	**<0.001**	0.635 (0.558 – 0.713)	**0.002**
PLR	0.592 (0.522 – 0.662)	**0.010**	0.511 (0.428 – 0.595)	0.787	0.561 (0.483 – 0.639)	0.118	0.508 (0.423 – 0.594)	0.845
MLR	0.516 (0.445 – 0.587)	0.654	0.516 (0.435 – 0.596)	0.708	0.503 (0.426 – 0.580)	0.936	0.499 (0.415 – 0.582)	0.977

PT (s)	0.625 (0.556 – 0.694)	**<0.001**	0.637 (0.558 – 0.715)	**0.001**	0.641 (0.567 – 0.714)	**<0.001**	0.646 (0.566 – 0.726)	**<0.001**
PTT (s)	0.575 (0.504 – 0.646)	0.037	0.617 (0.535 – 0.700)	**0.005**	0.604 (0.538 – 0.682)	**0.007**	0.576 (0.489 – 0.664)	0.075
BS (mg/dL)	0.581 (0.510 – 0.652)	**0.025**	0.619 (0.535 – 0.703)	**0.004**	0.617 (0.516 – 0.696)	**0.003**	0.653 (0.569 – 0.736)	**<0.001**
BUN (mg/dL)	0.580 (0.511 – 0.650)	**0.026**	0.623 (0.541 – 0.705)	**0.003**	0.592 (0.458 – 0.669)	**0.017**	0.644 (0.562 – 0.726)	**<0.001**
Cr (mg/dL)	0.498 (0.426 – 0.570)	0.958	0.598 (0.511 – 0.685)	**0.019**	0.538 (0.499 – 0.618)	0.332	0.590 (0.499 – 0.680)	**0.036**
AST (U/L)	0.653 (0.585 – 0.720)	**<0.001**	0.665 (0.586 – 0.743)	**<0.001**	0.657 (0.584 – 0.731)	**<0.001**	0.652 (0.571 – 0.733)	**<0.001**
ALT (U/L)	0.541 (0.470 – 0.611)	0.257	0.540 (0.460 – 0.620)	0.342	0.582 (0.506 – 0.658)	**0.036**	0.536 (0.454 – 0.618)	0.402
ALP (U/L)	0.452 (0.382 – 0.521)	0.180	0.496 (0.413 – 0.578)	0.915	0.527 (0.450 – 0.604)	0.489	0.539 (0.455 – 0.623)	0.365
LDH (U/L)	0.731 (0.670 – 0.792)	**<0.001**	0.735 (0.666 – 0.804)	**<0.001**	0.749 (0.683 – 0.814)	**<0.001**	0.710 (0.635 – 0.785)	**<0.001**
Alb (g/dL)	0.640 (0.573 – 0.706)	**<0.001**	0.632 (0.556 – 0.709)	**0.001**	0.666 (0.598 – 0.734)	**<0.001**	0.643 (0.567 – 0.719)	**<0.001**
ESR (mm/h)	0.584 (0.513 – 0.654)	**0.020**	0.600 (0.517 – 0.683)	**0.016**	0.557 (0.477 – 0.638)	0.141	0.615 (0.527 – 0.702)	**0.008**
pH	0.542 (0.470 – 0.614)	0.246	0.650 (0.569 – 0.731)	**<0.001**	0.630 (0.555 – 0.705)	**<0.001**	0.645 (0.563 – 0.728)	**<0.001**
PCO2 (mmHg)	0.592 (0.521 – 0.662)	**0.011**	0.611 (0.526 – 0.696)	**0.008**	0.595 (0.520 – 0.671)	**0.014**	0.604 (0.517 – 0.691)	**0.015**
HCO3 (mmol/L)	0.612 (0.541 – 0.684)	**0.002**	0.677 (0.595 – 0.759)	**<0.001**	0.674 (0.601 – 0.747)	**<0.001**	0.669 (0.588 – 0.750)	**<0.001**

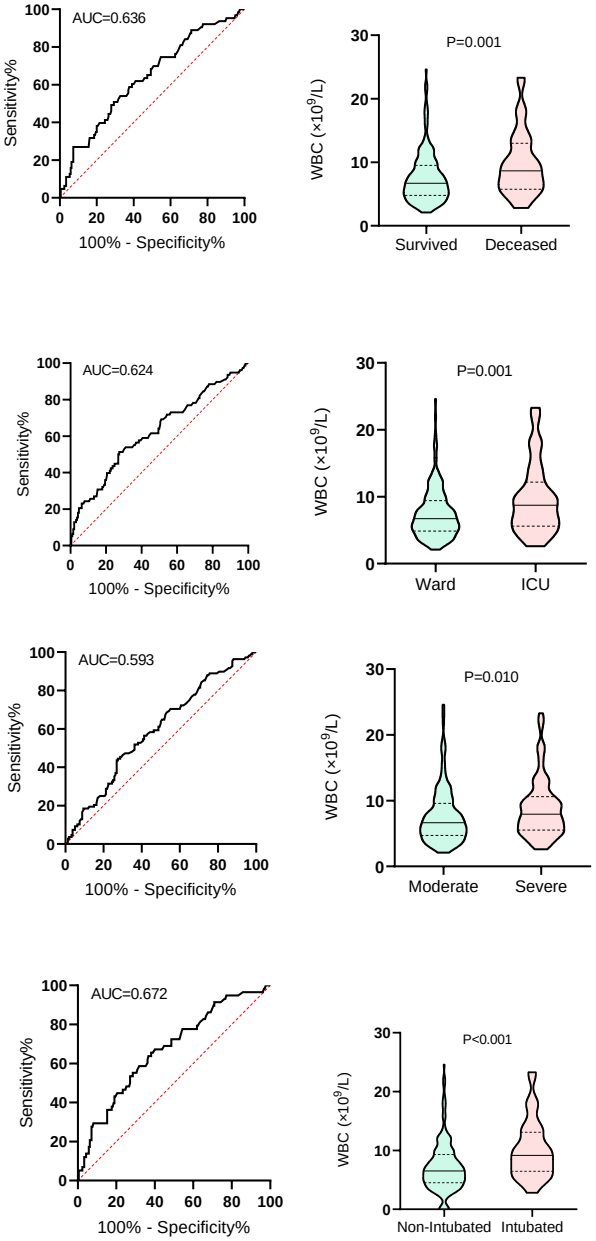
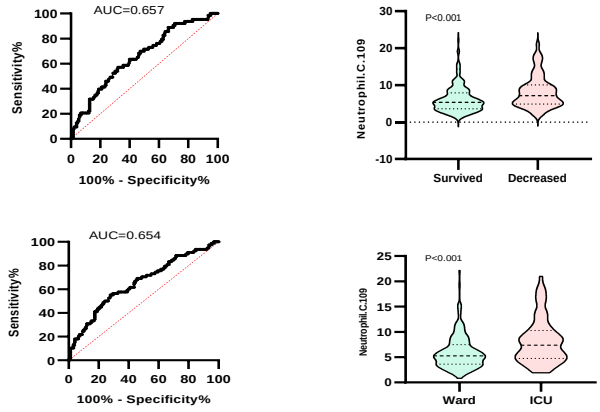


Figure 4. Predicting potential of WBC counts on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.



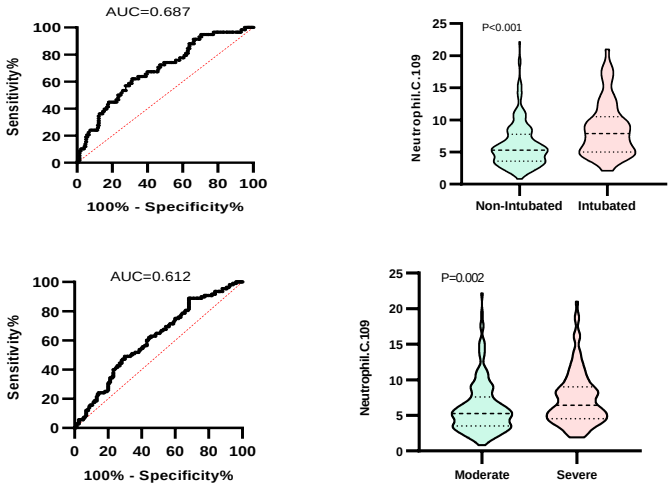


Figure 5. Predicting potential of neutrophil counts on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.

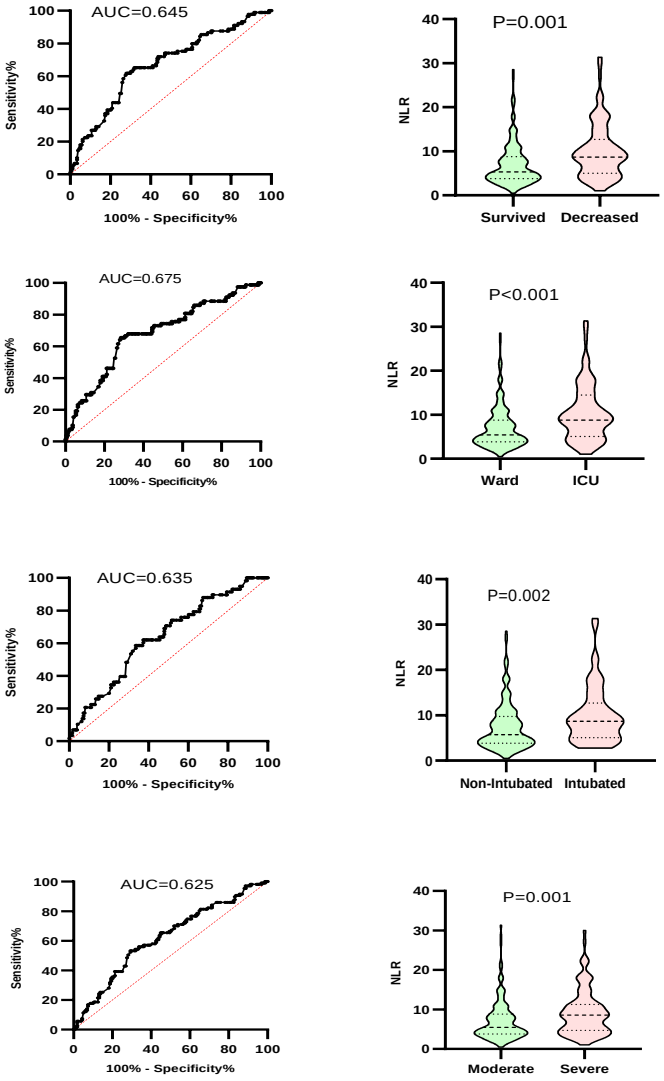


Figure 6. Predicting potential of NLR on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.

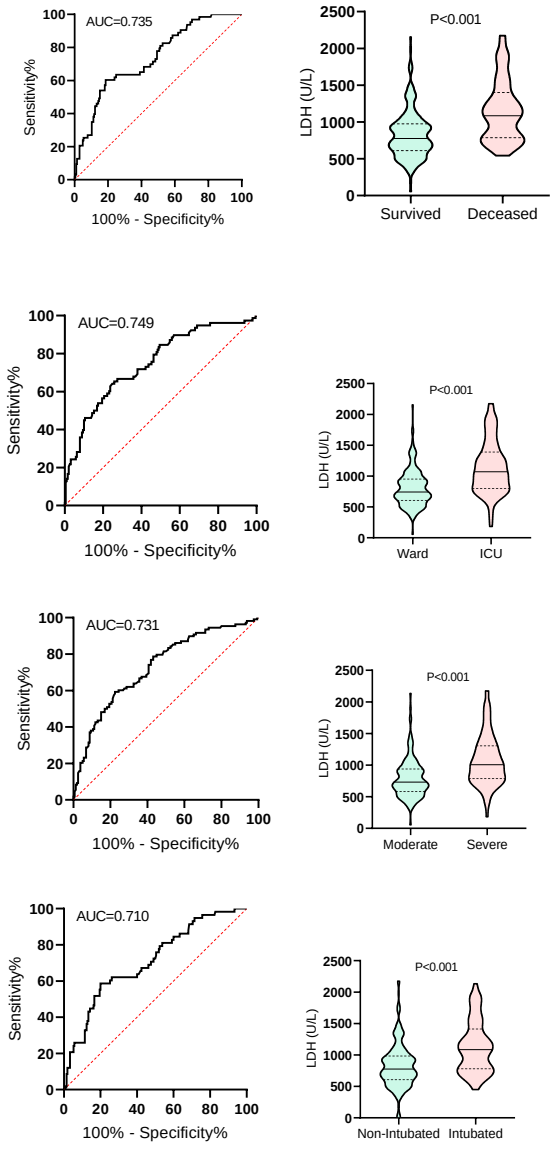
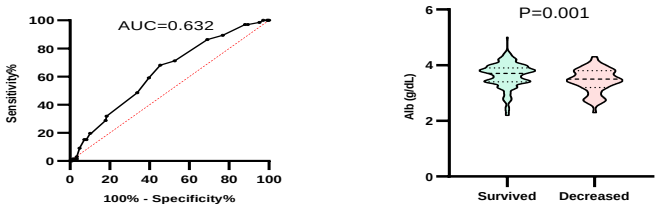


Figure 7. Predicting potential of LDH on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.



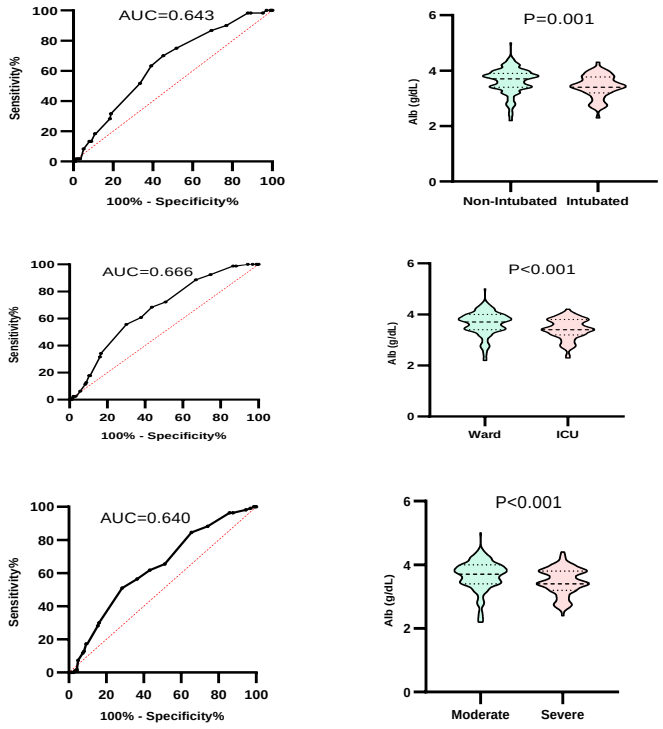


Figure 8. Predicting potential of serum Albumin levels on disease severity, ICU admission, requiring mechanical ventilation and death during hospitalization.

* ROC curve is shown on the left and Violin plot is shown on the right.

Discussion

In this study, we investigated 268 patients with mean age of 56 ± 16.6 years, of whom 59% were female. 39% of our patients had hypertension, 28% had diabetes mellitus, 11% had IHD, 4% had CKD and 4% had an underlying pulmonary disease.

In our study, WBC and neutrophil count was significantly higher in patients with severe disease, patients admitted to ICU, patients requiring mechanical ventilation and patients who died during hospitalizations; however, our findings didn't show any significant difference of lymphocyte count between the two groups of our study outcomes (in-hospital death, ICU admission, mechanical ventilation and disease severity). An elevated neutrophil count may be an indicator of viremia or a bacterial co-infection, which can worsen the severity and prognosis of infected patients (10, 11). Compensatory hyperplasia of the bone marrow which happens due to prolonged hypoxia can also result in elevated WBC count (12). A

meta analyze by Shi et al. suggested WBC count as a mortality predictor for COVID-19 (13). Many previous studies have shown elevated neutrophil and WBC counts, which supports our findings in this study (12, 14-21). Neutrophil infiltration in pulmonary capillaries in autopsy studies can confirm the role of neutrophil count in predicting disease severity and mortality (22, 23). In contrary to our findings, numerous previous studies have shown lymphopenia as a predicting factor of severity and different outcomes in COVID-19 (7, 16-21, 24-26). On the other hand, Zhou et al. demonstrated that after adjusting potential risk factors, lymphopenia didn't have a significant effect on COVID-19 mortality (11). We only included moderate and severe patients who met the admission criteria for COVID-19 disease in this study. This can lead to a similar lymphocyte count in all our patients. The mean lymphocyte counts of 1070, which indicates lymphopenia, can confirm this hypothesis. The presence of lymphopenia in our patients is similar to previous findings in the literature (5-7, 15, 27-30). Angiotensin converting enzyme 2, which is expressed in lymphocytes, is the main surface receptor for SARS-CoV-2 (31); this characteristic can result in serious damage to lymphocytes by the virus. Dramatically reduced lymphocyte (CD8, CD4 and CD3) count can indicate the effect of virus on T-lymphocytes and cause a major malfunction in immune system. Immunosuppression caused by lymphocyte injury will worsen the prognosis and can cause more severe disease (7, 13).

An elevated neutrophil count and decreased lymphocyte count results in an elevated NLR in the patients with more severe disease and poor prognosis. The fact of correlation between NLR and disease severity and outcome is stated by many previous studies (12, 20, 32-34).

In our study, LDH was significantly higher in patients with severe disease, patients admitted to ICU, patients requiring mechanical ventilation and patients who died during hospitalizations. The mentioned result is stated in previous studies, too (7, 12, 17-20, 35). It is evident that LDH can be a reflecting parameter for the extent of lung injury in ARDS, including the patients infected with corona virus SARS (36). We also showed that ESR is significantly higher in patients with severe disease, patients admitted to ICU, patients requiring mechanical ventilation and patients who died during hospitalizations. The correlation between inflammatory biomarkers including ESR and disease outcomes is noted in a meta-analysis by Shi et al. (13).

In our patients, serum levels of albumin were significantly lower in patients with severe disease, patients admitted to ICU, patients requiring mechanical ventilation and patients who died during hospitalizations. Bastug et al. also showed lower levels of albumin in patients with more severe disease (13, 17, 33). The relevance between the levels of serum albumin and ICU admission had been shown in MERS infection too (37). Lower levels of serum albumin may indicate the effect of malnutrition on disease prognosis and suggests the benefits of nutritional support (13).

In this study, AST levels were significantly higher in patients with severe disease, patients admitted to ICU, patients requiring mechanical ventilation and patients who died during hospitalizations; on the other hand, ALT levels were only higher in patients requiring ICU admission. There wasn't any significant difference in alkaline phosphatase in patients with different disease severity and outcomes. Altered liver function tests were documented in previous studies (17); however, other studies didn't show any significant change in liver enzymes among different stages of disease severity (20). There are studies showing that AST elevates before other liver enzymes, so it can be used for patients monitoring and predicting the disease outcome (13, 38). The direct effect of SARS-CoV-2 on cholangiocytes is suggested as a reason of liver failure in some recent studies. Liver injuries can occur as a result of drugs and systemic inflammatory response, too (39). The exact reason causing liver injuries should be investigated in further studies.

Our findings showed longer PT and PTT in patients with severe disease, patients admitted to ICU and patients who died during hospitalizations. PT was also longer in patients requiring medical ventilation. Alteration in coagulation factors is evident in previous studies (16-18); however, Wang et al. showed that there is no difference of PT, PTT and INR among disease severities. These results suggest that intravascular and consumption coagulopathies can be present in COVID-

19 patients with more severe disease and hence, lead to higher mortality rates (40). Previous studies on SARS indicate that inflammatory response may alter coagulation pathways and lead to disseminated infarcts and hemorrhages (41).

Based on the AUC of ROC curve we demonstrated that LDH, AST and serum albumin levels were the most powerful predicting factors for disease severity. LDH and serum albumin levels were also shown by Zhang et al. and HU et al. to be a potential predicting factor for disease severity (34, 42). We showed that LDH, WBC and neutrophil counts and NLR are significant predicting factor in ICU admission and requirement of mechanical ventilation. Previous studies support these results (33, 43).

Conclusion

This study shows higher values of hematologic indices in patients with severe disease and poor outcome. These indices can reflect inflammatory passages (neutrophilia) and viral infection by COVID-19 (lymphopenia). Evaluated inflammatory markers are also shown to be generally higher in patients with poor disease outcome. The existence of coagulopathies and altered LFT in patients with poor disease outcome can be the effect of direct viral infection of COVID-19 and needs to be further investigated.

Limitations

We evaluated patients with moderate and severe disease in this study. Evaluation of patients with mild disease will give us more accurate results. Also, a bigger sample size and a multicenter study can always help the accuracy of the survey. Determining the predicting factors can lead to earlier treatment for severe cases of COVID-19 and further studies to establish a cut-off for clinical interference can be clinically beneficial.

Author contribution

Conceptualization: **FN**, **AAF**; Methodology: **FN**, **BA**; Formal analysis and investigation: **AMGh**, **SM**; Writing - original draft preparation: **BA**, **ZCh**, **AMGh**; Writing - review and editing: **AMGh**, **FN**; Supervision: **FN**, **AAF**.

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Conflict of interest

There is no Conflicts of interest/competing interests.

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