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Research Article

Comparison of inflammation markers in different severities of COVID-19 disease

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Abstract

Objectives: We retrospectively analyzed COVID-19 patients for clinical and hematologic features and tried to define the most appropriate markers to diagnose and predict the severity.

Methods: This is a retrospective cross-sectional study. All 4443 patients included were diagnosed with reverse trancription-polymerase chain reaction between January 1 and December 30, 2020. We classified patients according to their mode of treatment: outpatient, inpatient in the ward, or inpatients in the intensive care unit (ICU).

Results: The mean age of 2283 (51.4%) women and 2160 (48.6%) men included in the study was determined to be 39.77±17.30. Of the 4443 patients, 3985 (89.7%) were outpatients, 330 (7.4%) were inpatients, and 128 (2.9%) patients were treated in the ICU. The mean hospital stay was 8.36±4.55 days for the survivors in the ward group and 2.67±1.53 days for those who died (p=0.031). The mean hospitalization time of the survivors in the ICU group was 19.97±12.09 days, and the mean hospitalization time of the deceased was 13.10±9.99 days (p=0.001). Age, ferritin, D-dimer, glucose, ALT, AST, urea, creatinine, CRP, HgA1c, IMG, IMG%, and RDW-SD showed a gradual and significant increase in outpatient, ward, and ICU groups (p<0.001). Na, K, Neu, Neu%, MCV, RDW-CV, MPV, NLR, PLR, and NMR increased gradually from the outpatient group to the service and ICU groups, whereas Ca, RBC, Hgb, and Hct values decreased significantly (p<0.001). WBC, lymph%, and RDW were highest in the ICU group.

Conclusion: Advanced age and being male are important risk factors for hospitalization. Indexes such as NLR, PLR, LCR, NMR, and LMR can be used to predict the severity of the disease.

Keywords: COVID-19, inflammation markers, LCR, NLR, PLR

COVID-19 patients are classified based on the severity of clinical symptoms as mild-to-moderate, severe, and critical and different measures are applied. As patients having mild symptoms may manifest respiratory problems by the second week although no initial treatment is required, all patients need to be observed closely. The WHO reports that approximately 80% of patients are considered mild-to-moderate, 13.8% of patients are severe, and 6.1% are critically ill. As the patients get older, the rate of mortality surges, and over the age of 80, the crude death rate reaches 21.9% [1]. Therefore, it is crucial to diagnose patients who might turn into severe or critical in the course of the disease. The routine hematologic tests include only basic parameters. If patients take part in a rigorous diagnosis, clinicians can get useful information.

Indicators that can be used to monitor the severity course of disease can significantly reduce patient death and thereby prevent the pandemic from getting worse.

In this study, we analyzed the differences between inflammatory markers of the different severity levels of COVID-19 patients to identify key laboratory markers for the diagnosis and treatment of the disease.

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Materials and Methods

Our study is a retrospective cross-sectional study. After taking approval from the Ministry of Health, it was approved by the Ethics Committee. All 4443 patients included in this study were tested positive for COVID-19 with reverse transcription-polymerase chain reaction using nasopharynx or pharynx swabs between January 1 and December 30, 2020. Patients with a history of metabolic, rheumatic, and malignant diseases and pregnant women were excluded from the study. We classified patients according to their mode of treatment: outpatient, inpatient in the ward, or inpatient in the ICU.

We processed the data of the patients obtained retrospectively from archived medical file from the hospital information system. We collected demographic data, signs and symptoms, accompanying diseases, and laboratory findings of the patients. CBC and other biochemical results were obtained on application to the outpatient clinic or first results on admission to the ward or ICU.

General characteristics of the study groups were identified by descriptive analyses. Mean±standard deviation is used for continuous variables. n (%) defines data on categorical variables. Between groups, quantitative variable means were compared using the Significance test of the difference between two means and Mann Whitney U test for the normally distributed and non-normally distributed variables, respectively. For within-group comparison, the Wilcoxon test and the significance test of the difference between the two groups were used for non-normally and for normally distributed variables, respectively. Qualitative variables relations were evaluated using the Chi-square test. With Pearson's correlation, the correlation coefficient of quantitative variables was determined. To interpret statistical significance, p values of less than 0.05 were used. For calculation, ready-made statistics software was used (SPSS 22.0, Chicago, IL, USA).

Results

The distribution of qualitative variables by hospitalization groups is given in Table 1.

Of the total patients, 3985 (89.7%) patients applied as outpatients, 330 (7.4%) patients received treatment in the ward, and 128 (2.9%) patients received treatment in the ICU. While 52.4% of the outpatients were female, 54.2% of those in the ward were men, and 64.8% of those in the ICU were men. While females were significantly higher than males in the outpatient group ($p<0.001$), males were significantly higher than females in the ward and ICU group ($p<0.001$). The duration of hospitalization in the ward (8.31±4.56 days) and that in the ICU (15.24±12.72 days) were found to be significantly correlated with each other ($p<0.001$). A Rh (+) and then 0 Rh (+) were seen the most while B Rh(-) and AB Rh(-) blood groups were seen the least in all outpatients and inpatients. There was no significant difference between the groups regarding blood groups ($p=0.525$). The number of males with vitamin D deficiency was significantly higher than females ($p<0.001$). There was no significant difference in vitamin D deficiency between inpatients and outpatients ($p=0.196$). One outpatient (0.0%), 3 patients in the ward (0.1%), and 94 patients in the ICU (73.4%) died, and the difference between them was significant ($p<0.001$). Among those who lost their lives, males were significantly higher than females ($p=0.003$). There was a significant difference between all three groups regarding DM, asthma, and cardiovascular disease (CVD) ($p<0.001$, $p<0.001$, $p<0.001$, respectively). The mean hospital stay was 8.36±4.55 days for the survivors and 2.67±1.53 days for those who died in the ward group ($p=0.031$). The mean hospitalization time of the survivors and the deceased was 19.97±12.09 days 13.10±9.99 days, respectively ($p=0.001$).

Age, ferritin, D-dimer, glucose, ALT, AST, urea, creatinine, CRP, HgA1c, IMG, IMG%, and RDW-SD showed a gradual and significant increase in the outpatient, ward, and ICU groups ($p<0.001$). Na, K, Neu, Neu%, MCV, RDW-CV, MPV, NLR, PLR, and NMR increased from outpatient to ward and ICU groups. WBC, lymph%, and RDW were highest in the ICU group. LMR, lymph, MCHC, and LCR were found the lowest in the ICU group. Significant associations were found between outpatient and ICU and ward and ICU for all except LCR ($p<0.001$). Considering LCR, significant differences were found between outpatient and ward groups and the outpatient and ICU groups ($p<0.001$). NER was found to be highest in the ICU group, which showed a significant relationship with the other groups ($p<0.001$). Mon%, RBC, Hgb, and Hct were significantly lower in the ICU group. Ca, RBC, Hgb, and Hct values decreased significantly in all three groups from the outpatient group to the ICU group ($p<0.001$). Cl was the lowest in the ward group, with a significant difference in all three groups ($p<0.001$). The distribution of quantitative variables by groups is given in Table 2.

ROC analysis of NLR, PLR, LCR, NMR, LMR, and NER indexes are given in Table 3 and ROC curves are given in Figures 1 and 2.

Discussion

The mean age of 2283 (51.4%) women and 2160 (48.6%) men included in the study. The mean ages for outpatient, ward and ICU groups were 37.51±15.29, 54.84±21.75, and 71.38±11.99, respectively. Disease severity has been shown to be related to age, and this shows that as we age, the body's defenses decrease due to the deterioration of immune and physiological functions [2]. Our study showed that patients in their forties overcame the disease with outpatient treatment, whereas patients in their sixties received inpatient treatment in the ward and those over seventy years received treatment in the ICU. Among the outpatients, women were significantly higher than men ($p<0.001$). Males were significantly higher than females in both the ward and ICU groups ($p<0.001$). Comorbidities such as hypertension (HT), asthma, lower respiratory tract infection (LRTI), upper respiratory tract infection (URTI), endocrine problems such as DM, psychiatric problems, and vitamin D deficiency were found lowest in the outpatient group

Table 1. Distribution of qualitative variables by hospitalization groups

	Group			p
	Outpatient n (%)	**Ward n (%)**	**ICU n (%)**	
Gender				
Female	2087 (52.4)[a]	151 (45.8)[ab]	45 (35.2)[b]	<0.001
Male	1898 (47.6)[a]	179 (54.2)[ab]	83 (64.8)[b]	
Intensive care unit (ICU)				
None	3985 (100)[a]	330 (100)[a]	0 (0)[b]	<0.001
Present	0 (0)[a]	0 (0)[a]	128 (100)[b]	
Emergency department application				
None	0 (0)[a]	2 (0.6)[b]	1 (0.8)[b]	<0.001
Present	3985 (100)[a]	328 (99.4)[b]	127 (99.2)[b]	
Blood groups				
A RH (+)	1762 (44.7)	147 (45.1)	53 (41.4)	0.525
B RH (+)	555 (14.1)	39 (12)	19 (14.8)	
AB RH (+)	271 (6.9)	30 (9.2)	6 (4.7)	
0 RH (+)	868 (22)	81 (24.8)	32 (25)	
A RH (-)	263 (6.7)	17 (5.2)	11 (8.6)	
B RH (-)	66 (1.7)	4 (1.2)	1 (0.8)	
AB RH (-)	51 (1.3)	1 (0.3)	3 (2.3)	
0 RH (-)	110 (2.8)	7 (2.1)	3 (2.3)	
RH antigen types				
Negative	490 (12.4)	29 (8.9)	18 (14.1)	0.142
Positive	3456 (87.6)	297 (91.1)	110 (85.9)	
Blood antigen types				
A	2025 (51.3)	164 (50.3)	64 (50)	0.793
B	621 (15.7)	43 (13.2)	20 (15.6)	
AB	322 (8.2)	31 (9.5)	9 (7)	
0	978 (24.8)	88 (27)	35 (27.3)	
Survival				
Survived	3984 (100)[a]	327 (99.1)[b]	34 (26.6)[c]	<0.001
Died	1 (0)[a]	3 (0.9)[b]	94 (73.4)[c]	
Computed tomography (CT) images				
Incompatible	3822 (95.9)[a]	187 (56.7)[b]	78 (60.9)[b]	<0.001
Compatible	163 (4.1)[a]	143 (43.3)[b]	50 (39.1)[b]	
Hypertension (HT)				
None	3479 (87.3)[a]	212 (64.2)[b]	49 (38.3)[c]	<0.001
Present	506 (12.7)[a]	118 (35.8)[b]	79 (61.7)[c]	
Lower respiratory tract infection (LRTI)				
None	3635 (91.2)[a]	249 (75.5)[b]	85 (66.4)[b]	<0.001
Present	350 (8.8)[a]	81 (24.5)[b]	43 (33.6)[b]	
Upper respiratory tract infection (URTI)				
None	3957 (99.3)[a]	329 (99.7)[b]	127 (99.2)[b]	<0.001
Present	28 (0.7)[a]	1 (0.3)[b]	1 (0.8)[b]	
Pain				
None	3665 (92)[a]	293 (88.8)[ab]	109 (85.2)[b]	0.004
Present	320 (8)[a]	37 (11.2)[ab]	19 (14.8)[b]	
Cardio-vascular disease (CVD)				
None	3728 (93.6)[a]	262 (79.4)[b]	79 (61.7)[c]	<0.001
Present	257 (6.4)[a]	68 (20.6)[b]	49 (38.3)[c]	

Table 1. Cont.

	Group			p
	Outpatient n (%)	Ward n (%)	ICU n (%)	
Urinary Tract Problems				
None	3810 (95.6)[a]	280 (84.8)[b]	88 (68.8)[c]	<0.001
Present	175 (4.4)[a]	50 (15.2)[b]	40 (31.3)[c]	
Diabetes Mellitus (DM)				
None	3724 (93.5)[a]	278 (84.2)[b]	81 (63.3)[c]	<0.001
Present	261 (6.5)[a]	52 (15.8)[b]	47 (36.7)[c]	
Orthopedical Problems				
None	3481 (87.4)[a]	256 (77.6)[b]	94 (73.4)[c]	<0.001
Present	504 (12.6)[a]	74 (22.4)[b]	34 (26.6)[c]	
Epilepsy, Migraine				
None	3891 (97.6)	324 (98.2)	123 (96.1)	0.418
Present	94 (2.4)	6 (1.8)	5 (3.9)	
Surgical Problem				
None	3908 (98.1)	323 (97.9)	123 (96.1)	0.288
Present	77 (1.9)	7 (2.1)	5 (3.9)	
Endocrine Problems				
None	3494 (87.7)[a]	250 (75.8)[b]	65 (50.8)[c]	<0.001
Present	491 (12.3)[a]	80 (24.2)[b]	63 (49.2)[c]	
Psychiatric Problems				
None	3722 (93.4)	301 (91.2)	113 (88.3)	0.030
Present	263 (6.6)	29 (8.8)	15 (11.7)	
Vit D Deficiency				
None	3949 (99.1)[a]	328 (99.4)[a]	123 (96.1)[b]	0.002
Present	36 (0.9)[a]	2 (0.6)[a]	5 (3.9)[b]	

Pearson chi-square test was used. [ab]: The common letter as a row indicates statistical insignificance between the column ratios.

and highest in the ICU group. Vitamin D deficiency was lowest in the service group and highest in the ICU group. These results show that the underlying diseases are more common in elderly patients and increase the severity of the disease and hence admission to the hospital in the course of the disease. In our study, 98 (2.2%) of the patients died. Our mortality rate was determined as 2.2%. The mortality rate of the patients was significantly highest in the ICU group and the lowest in the outpatient group. The death rate was significantly higher for men than women (p=0.003). The mean duration of hospitalization was 15.2 days in the ICU group, which was significantly higher than the mean of 8.3 days in the ward group. The mean hospital stay was 8.36±4.55 days for the survivors in the ward group and 2.67±1.53 days for those who died (p=0.031). The mean hospitalization time of the survivors in the ICU group was 19.97±12.09 and the mean hospitalization time of the deceased was 13.10±9.99 days (p=0.001). Aktoz et al. [3] reported that the median time from the onset of symptoms to discharge from hospital was 22 days in hospitalized patients. They stated that mortality is quite high in patients requiring intensive care, and the median time from the onset of symptoms to death is 14 days. Yang et al. [4] reported that the median time from the onset of the symptom to hospital admission was 10.0 (IQR, 7.0-13.0) days, which tended to be longer than those who recovered [9.0 (IQR, 6.0-12.0) days].

In our study, the biochemical parameters of the patients were evaluated in detail. Glucose and HgA1c values of the patients showed a significant gradual increase in all three groups from outpatient to ICU (p<0.001). Determining the HbA1c level after hospitalization helps evaluate the inflammation, hypercoagulation, and prognosis of COVID-19 patients. In COVID-19 cases, serum ferritin level, CRP level, and inflammation markers such as ESR and coagulation factor fibrinogen (Fbg) correlate positively with HbA1c level.

Former studies have indicated that abnormal immune system function can be caused by diabetes. Wang et al. [5] reported that inflammation and hypercoagulability are related to high HbA1c level in COVID-19 patients, and diabetic patients have a higher mortality rate (27.7%).

Tezcan et al. [6] reported that the most common electrolyte abnormality was hyponatremia. More frequent requirements for ICU and mechanical ventilation, higher mortality rate, and longer hospitalization were seen in patients with hyponatremia,

Table 2. Distribution of quantitative variables by hospitalization group

Variables	n	Total	Group			p
			Outpatient	Ward	ICU	
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age (Years)	4443	39.77±17.3	37.51±15.29[a]	54.84±21.75[b]	71.38±11.99[c]	<0.001
Hospt. Days (Days)	450	10.28±8.4	-	8.31±4.56	15.24±12.72	<0.001
Ferritin (ml/ng)	3289	155.86±335.15	107.71±231.23[a]	274.4±428.51[b]	987.91±726.04[c]	<0.001
D Dimer (ng/ml)	1487	0.63±0.97	0.46±0.75[a]	0.69±0.93[b]	2.07±1.44[c]	<0.001
Glucose(mg/dl)	4296	111.13±48.22	107.76±43[a]	122.95±56.44[b]	182.22±93.88[c]	<0.001
ALT (U/L)	4290	31.55±85.45	27.51±40.45[a]	43.66±174.17[b]	121.52±331.08[c]	<0.001
APTT (second)	1455	31.36±8.95	30.87±6.7[a]	32.68±8.98[b]	80.71±54.63[c]	<0.001
AST (U/L)	4290	37.12±201.06	27.2±62.99[a]	53.71±367.38[b]	291.57±909.97[c]	<0.001
Urea (mg/dL)	4290	31.84±27	28.84±17.36[a]	36.32±27.3[b]	110.15±84.23[c]	<0.001
CRP (mg/L)	2698	9.58±30.84	6.06±19.3[a]	25.72±49.39[b]	59.43±94.68[c]	<0.001
Fibrinogen (mg/dL)	2425	325.21±89.97	319.23±85.41[a]	332.67±86.82[a]	410.19±120.48[b]	<0.001
HbA1c %	2016	6.18±1.47	6.06±1.33[a]	6.74±1.68[b]	7.61±2.45[c]	<0.001
Calcium (mg/dL)	4114	9.38±0.67	9.46±0.57[a]	9.08±0.82[b]	7.94±0.91[c]	<0.001
Chlorine (mmol/L)	3653	103.82±3.67	103.82±3.37[a]	103.01±4.05[b]	105.91±7.37[c]	<0.001
Creatinine (mg/dL)	4294	0.8±0.61	0.75±0.44[a]	0.92±0.85[b]	2.09±1.69[c]	<0.001
LDH (U/L)	3056	251.03±416.24	219.84±124.78[a]	307.8±806.01[b]	756.46±1415.42[c]	<0.001
Potassium (mmol/L)	4147	4.3±0.47	4.29±0.42[a]	4.3±0.53[a]	4.66±1.1[b]	<0.001
Procalcitonin (ng/mL)	108	3.05±10.8	0.85±1.66	0.23±0.33	5.18±14.67	0.104
PT (second)	2899	12.81±5.09	12.47±2.69[a]	12.74±2.44[a]	19.72±19.79[b]	<0.001
INR	3088	1.04±0.42	1.01±0.23[a]	1.03±0.21[a]	1.55±1.68[b]	<0.001
Sodium (mmol/L)	4157	139.21±3.18	139.06±2.89[a]	139.47±3.39[a]	142.94±6.53[b]	<0.001
Vitamin D (IU)	1400	16.1±11.08	16.15±11.22	16.39±9.95	13.8±8.84	0.393
WBC (10^3/mL)	780	8.11±4.88	7.01±2.62[a]	6.9±2.95[a]	13.95±8.09[b]	<0.001
NEU (10^3/µL)	707	6.02±5.02	4.63±2.32[a]	4.77±2.93[a]	12.57±8.05[b]	<0.001
LYM (10^3/µL)	706	1.53±0.96	1.68±0.9[a]	1.6±0.97[a]	0.96±0.88[b]	<0.001
MON (10^3/µL)	706	0.53±0.28	0.55±0.22[a]	0.49±0.2[b]	0.56±0.5[a]	0.021
EOS (10^3/µL)	606	0.1±0.13	0.09±0.1	0.11±0.14	0.11±0.18	0.208
BAS (10^3/µL)	544	0.02±0.01	0.02±0.01[a]	0.02±0.01[a]	0.02±0.02[b]	0.023
IG (10^3/µL)	707	0.12±0.35	0.03±0.04[a]	0.1±0.21[b]	0.38±0.73[c]	<0.001
NEU %	707	68.35±15.23	64.57±12.79[a]	65.4±13.91[a]	85.14±12.85[b]	<0.001
LYM %	706	22.77±13.26	25.54±11.72[a]	25.39±12.56[a]	9.29±10.25[b]	<0.001
MON %	706	7.41±3.41	8.43±3.41[a]	7.49±2.73[b]	4.45±3.13[c]	<0.001
EOS %	622	1.44±1.65	1.26±1.16[ab]	1.68±1.9[b]	1.4±2.17[a]	0.014
BAS %	574	0.29±0.19	0.3±0.19	0.28±0.18	0.3±0.28	0.519
IMG %	707	1.04±1.99	0.44±0.41[a]	1.22±2.39[b]	2.24±2.78[c]	<0.001
RBC (10^6/µL)	780	4.39±0.71	4.67±0.51[a]	4.4±0.65[b]	3.65±0.77[c]	<0.001
HGB (gr/dL)	780	12.64±2.15	13.4±1.81[a]	12.67±1.95[b]	10.54±2.11[c]	<0.001
HCT %	780	37.98±6.01	40.03±4.88[a]	37.99±5.5[b]	32.42±6.43[c]	<0.001
MCV (fL)	780	86.75±6.52	85.9±6.57[a]	86.66±6.1[a]	89.26±6.8[b]	<0.001
MCH (pg)	780	28.85±2.58	28.74±2.66	28.9±2.48	29.05±2.58	0.484
MCHC (gr/dL)	780	33.24±1.11	33.42±0.95[a]	33.32±1.07[a]	32.54±1.35[b]	<0.001
RDW-CV (fL)	780	14.08±1.8	13.65±1.35[a]	13.95±1.74[a]	15.53±2.24[b]	<0.001
RDW-SD (fL)	780	44.28±5.56	42.61±3.78[a]	43.74±5.16[b]	50.06±6.67[c]	<0.001
PLT	780	231.65±92.03	223.91±69.87[a]	249.87±98.54[b]	208.62±117.45[a]	<0.001
MPV (fL)	778	10.14±1.24	9.95±1.1[a]	9.99±1.14[a]	11.03±1.46[b]	<0.001
PDW (fL)	778	15.9±1.41	15.91±1.16[a]	15.68±1.7[a]	16.43±1.07[b]	<0.001
PCT %	778	0.23±0.08	0.22±0.06[a]	0.24±0.09[b]	0.22±0.11[a]	0.001

Table 2. Cont.

Variables	n	Total	Group			p
			Outpatient	Ward	ICU	
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	
PLCC (%)	708	59.03±24.26	54.82±19.26[a]	61.93±25.23[b]	63.85±31.45[b]	<0.001
PLCR (%)	708	27.04±8.9	25.37±7.7[a]	25.98±8.09[a]	33.93±10.39[b]	<0.001
NLR	706	7.5±15.15	3.62±3.06[a]	4.08±4.34[a]	25.75±30.17[b]	<0.001
PLR	706	222.16±413.54	163.2±89.59[a]	195.82±135.98[a]	441.85±952.17[b]	<0.001
LCR	526	2.08±4.99	3.11±6.26[a]	1.46±3.65[b]	0.69±2.73[b]	<0.001
NMR	706	13.25±14.64	9.18±4.83[a]	10.37±5.95[a]	30.8±27.78[b]	<0.001
LMR	706	3.32±2.13	3.42±1.94[a]	3.66±2.23[a]	2.26±2.07[b]	<0.001
NER	606	177.2±324.03	112.58±128.63[a]	124.21±237.08[a]	500.95±608.22[b]	<0.001

One-way ANOVA was used. [abc]: For rows: A common letter in the same row indicates statistical insignificance. ICU: Intensive care unit; Hospt. days: Hospitalization days; ALT: Alanine aminotransferase; APTT: Activated partial thromboplastin clotting time; CRP: C-reactive proteine; LDH: Lactate dehydrogenase; PT: Prothrombin time; WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MON: Monocyte; EOS: Eosinophil; BAS: Basophil; IG: Immature granulocyte; RBC: Red blood cell; HGB: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW-CV: Red cell distribution width-coefficient of variation; RDW-SD: Red cell distribution width-Standard deviation; PLT: Platelet; PDW: Platelet distribution width; PCT: Platelet crit; PLCC: Platelet large cell coefficient; PLCR: Platelet large cell ratio; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; LCR: Lymphocyte C-reactive protein ratio; NMR: Neutrophil monocyte ratio; LMR: Lymphocyte monocyte ratio; NER: Neutrophil eosinophil ratio.

Table 3. Results of ROC analysis

Variable	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	p
NLR	≥6.938	0.9499	0.9239	0.8762	0.528	0.9872	<0.001
PLR	≥255.556	0.7213	0.6196	0.8176	0.3373	0.9348	<0.001
LCR	≤0.212	0.7783	0.8031	0.6413	0.2431	0.9578	<0.001
NMR	≥16.227	0.9362	0.8587	0.9039	0.5725	0.9771	<0.001
LMR	≤1.733	0.7769	0.6848	0.8013	0.3405	0.9443	<0.001
NER	≥162.8	0.8207	0.6866	0.8182	0.3194	0.9545	<0.001

ROC: Receiver operating characteristic; AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; LCR: Lymphocyte C-reactive protein ratio; NMR: Neutrophil monocyte ratio; LMR: Lymphocyte monocyte ratio; NER: Neutrophil eosinophil ratio.

hypochloremia, or hypocalcemia. Death from COVID-19 was associated with hyponatremia independently. Significantly low levels of sodium and potassium were reported in meta-analyses of severe COVID-19 patients [7]. In our study, Na, K, and Cl values showed a significant gradual increase in all three groups from outpatient to ICU. Osman et al. [8] found that hypocalcemic patients had longer hospitalization time. Patients with hypocalcemia had worse ordinal scale, CRP, lymphopenia, LDH, ICU admission, longer hospital stay, higher oxygen requirements, and ARDS. In our study, Ca decreased gradually from the outpatient group to the ICU group. Vitamin D was lowest in the ward group and highest in the ICU group.

Liver injury pathogenesis in SARS-COV-2 infection may be caused by a flare-up of preexisting liver disease, virus-induced cytopathic effects, hypoxemia, drug damage, and overresponsive inflammatory processes. Gan et al. [9] reported that severe COVID-19 cases had a significantly higher incidence of liver function test (LFT) abnormality than non-severe cases. As high expression of ACE2 is in cardiac blood vessels, we expect increased levels of LDH in COVID-19 patients. CRP is produced primarily in the liver, which is a well-known biochemical marker of acute inflammation. In our study, LFT, ALT, AST, and LDH values showed a significant gradual increase in all three groups from outpatient to ICU (p<0.001).

Chu et al. [10] reported that 36 (6.7%) of 536 SARS patients had acute kidney injury (AKI). In a study, AKI was seen in 8 (26.7%) of 30 patients with MERS-CoV infection [11]. Na et al. [12] reported that AKI was seen in 3 (4.5%) of the 66 patients diagnosed with COVID-19, and all 3 patients recovered after hemodialysis. In our study, the values of urea and creatinine showed a significant gradual increase in all three groups from outpatient to ICU, suggesting AKI (p<0.001).

Comparing patients in the ICU with patients with milder symptoms, a lot of inflammation markers are increased including leukocyte count, ferritin C-reactive protein (CRP), D-dimer, prothrombin, procalcitonin (PCT), and lactate dehydrogenase (LDH). It has been observed in a meta-analysis that increased PCT makes patients nearly fivefold more likely for severe infec-

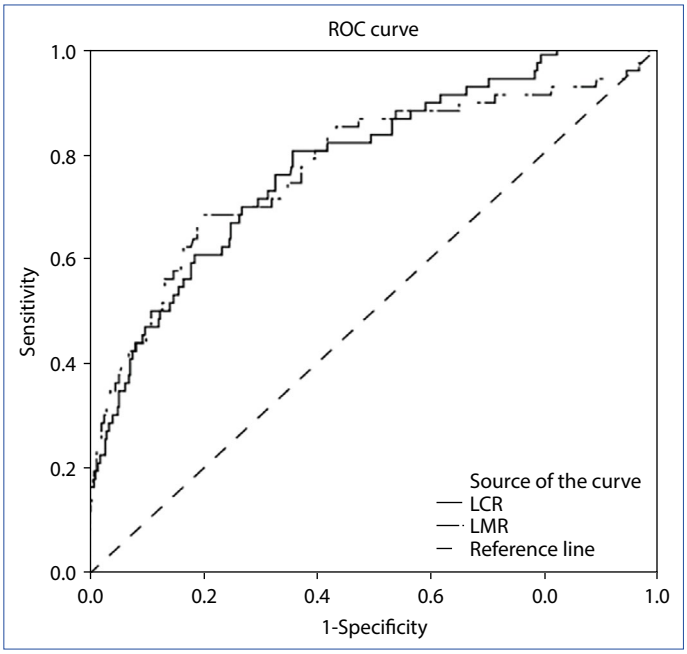

Figure 1. ROC curves for LCR and LMR.

ROC: Receiver operating characteristic; LCR: Lymphocyte/C-reactive protein ratio; LMR: Lymphocyte/monocyte ratio.

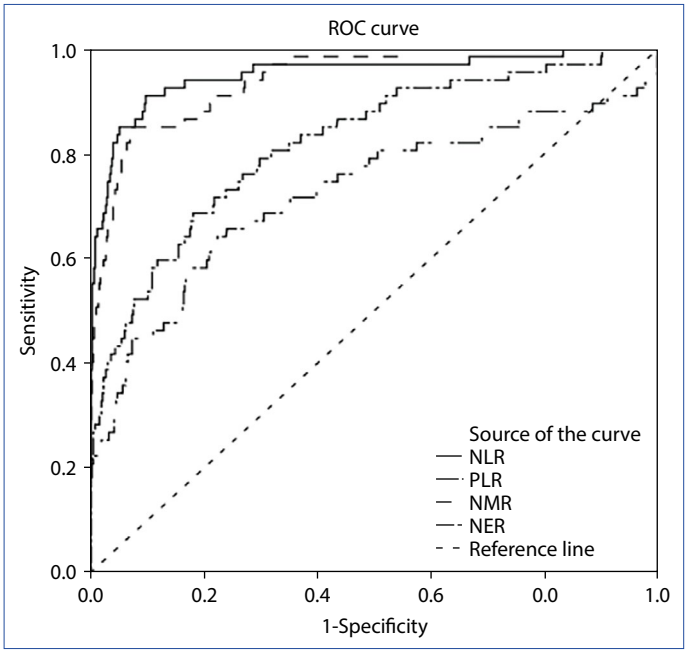

Figure 2. ROC curves for NLR, PLR, NMR, and NER.

ROC: Receiver operating characteristic; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; NMR: Neutrophil/monocyte ratio; NER: Neutrophil/eosinophil ratio.

tion [13]. Although the existing literature has not been totally consistent on which markers may be helpful, if we observe inflammatory marker levels, they can help us to predict the progression of the disease. For instance, few studies reported that contrary to the expectation, white blood cell count is similar or even lower in severe disease than in mild disease [14, 15]. To intervene in COVID-19 progression on time, monitoring inflammatory markers is very important. The increase of inflammatory markers in circulation for COVID-19 are very similar to the increase in ordinary infections, such as elevated levels of PCT, released into the circulation on bacterial infection, in peripheral blood correlate with infection severity. Meta-analysis of Ji et al. [16] showed increased levels of WBC, CRP, erythrocyte sedimentation rate (ESR), PCT, IL-10, and IL-6 in patients with severe disease. Significantly higher levels of WBC, PCT, CRP, IL-6, and ESR were seen in patients who died than in survivors during the follow-up. Higher levels of inflammatory markers were seen in severe cases than milder ones. Monitoring these markers may allow early prediction of the disease. In their study, Kim et al. [17] found high CRP levels in COVID-19 patients. In dead patients of COVID-19, especially in the first 3 days after being admitted to the hospital, significantly increased neutrophils and sepsis were determined. The rapid progress of the disease to death could be associated with secondary infection. Patients suspected of secondary bacterial infections should be monitored for bacterial infection indicators such as PCT, and antibiotics should be administered early. Comparing patients who died within the first 3 days of admission with the rest of the dead patients, prothrombin time (PT) was prolonged, D-dimer was determined to be highly elevated, and platelet counts were low, showing coagulation disturbance and tendency to disseminated intravascular coagulation in the former group. Consistent with the studies mentioned above, in our study, the values of inflammation markers such as WBC, ferritin, D-dimer, prothrombin, CRP, PT, INR, fibrinogen, and LDH showed a significant gradual increase in all three groups from outpatient to ICU. Procalcitonin values were the lowest in the ward group and the highest in the ICU group.

WBC frequently increased in severe cases and more frequently in critical patients; however, in COVID-19 patients, WBC was low or normal. The same was found in asymptomatic patients. Compared to survivors, leukocytosis (related to ICU admission) was more frequent in non-survivors [13]. On the contrary, reduced count of WBC was reported by Shi et al. [18] in mild and severe cases. To determine whether WBC count may be used as a prognostic parameter remains a question. Li et al. [19] suggested that WBC counts had no prognostic value because of diversity in cases. Leukocytosis is dependent on many factors such as co-infections to medications like prednisone or to the variability of the immune response. In our study, WBC was highest in the ICU group, then in the outpatient group, and lowest in the ward group.

Neutrophilia is present in most severe cases. In severe COVID-19 patients, neutrophilia is observed during admission to the hospital. Hu et al. [20] showed that variability of neutrophilia even within the severe group was observed. Non-survivors have higher neutrophil counts compared to survivors. In our study, Neu ve Neu% gradually increased from outpatient group to ICU. In contrast, Zheng et al. [21] observed a significant decrease of granulocytes in severe cases compared

to non-severe ones. In the study of Guan et al. [22], 83.2% of 1099 patients were admitted with lymphopenia, and in severe patients, lymphopenia was even more outstanding. Many studies reported that there were patients with both leukopenia and lymphopenia, but lymphopenia was more predominant in adolescents, adults, and the elderly. During the course of COVID-19 infection, dynamic change of lymphocyte percentage was reported by Wang et al. [23]. ICU admissions and death were related to more severe lymphopenia. Consistent with the above findings, in our study, Lym and Lym% values were found to be the lowest in the ICU group. Even though some studies could not find any difference, in severe cases, monocyte numbers were in the lower range [24]. In a few studies, even though monocyte count was still within the normal range, in COVID-19 patients, a higher monocyte count was seen compared to healthy individuals [25]. In our study, the lowest Mon values were observed in the ward group. Mon% was significantly the highest in the outpatient group, followed by the ward, and the lowest in the ICU group.

In severe COVID-19 patients, it has been observed that NLR is seen to be consistently elevated. Furthermore, the prognostic value of the NLR was shown in a few studies. In COVID-19 patients, a higher NLR on admission was demonstrated to be an independent predictor of severe pneumonia [26]. Zhang et al. [27] reported that 94% of the 82 deceased patients with COVID-19 had an NLR >5. Increased NLR could be used as a tool to identify patients who have a high risk of admission because of its consistency and proven importance. Besides NLR, NMR was found to be significantly elevated in pneumonia patients, but it has not been proven as a strong prognostic factor for COVID-19 patients [25]. In our study, we determined mean NLRs of 3.62, 4.08, and 25.75 for outpatient, ward, and ICU groups, respectively. We found a cut-off value of ≥6938 to have ICU care due to severe illness for NLR. We found a cut-off value for NMR of ≥162.80, indicating disease severity and need for ICU care.

Eosinopenia has been reported in 50-70% of severe COVID-19 patients. Eosinophilic inflammation was observed in a minority of COVID-19 infections. Liu et al. [28] reported that in a small cohort of patients, eosinopenia was present on admission to the hospital, improved compared to admission upon discharge. In line with these studies, Katar et al. [29] indicated eosinopenia at the time of presentation. Eos counts, after 1 week of treatment, improved significantly compared with the level during admission (p=0.004). Eos values were found to be the lowest in the outpatient group. In our study, we also determined a cut-off value for NER of ≥162.8, indicating disease severity and the need for ICU care.

In some studies, 41-50% of elderly cases had low normal concentrations of hemoglobin (Hb) on admission [13]. With disease progression, a decrease of Hb was observed by Zheng et al. [30] in another study. In adult COVID-19 patients, the mean corpuscular volume (MCV) was lower and the mean corpuscular hemoglobin concentration (MCHC) was significantly higher when compared with healthy individuals [25]. This is most probably because of decreased hemoglobin. In COVID-19 patients, red cell distribution width (RDW) has also increased. At the onset of disease, COVID-19 patients had low levels of MCV as well as RBC, Hb, HCT, and MCHC. Decreases in hemoglobin in severe COVID-19 cases may be due to both inflammation and direct infection of precursor cells by the virus itself. Inflammation impairs the function in maturing erythrocytes and results in impaired hemoglobin production [31]. In our study, RBC, Hb, HCT, and MCHC values were found to be the lowest in the ICU group. MCV has increased from the outpatient group to the service and ICU groups.

In general, compared with non-severe cases, severe cases had lower platelet (PLT) counts on admission. In the last 24 h before death, platelet counts of <100×109/L in 60% of patients were reported by Zhang et al. [27]. Hu et al. [20] observed thrombocytopenia in 12.5% of the most critical cases and with 6.4% of the less severe patients. A small study including 30 COVID-19 patients conducted by Lippi et al. [32] summarized that low PLTs had already been related to poor prognosis. In old patients and those with longer hospitalization, a peak in PLT numbers was determined. In COVID-19 patients, high MPV is caused by increased release of higher volume of young PLTs together with macrothrombocytes due to higher PLT turnover. The severity of the infection may also be indicated by PLR. The difference in PLR on admission and the maximum value during treatment in 30 hospitalized patients was described by Qu et al. [33]. A cut-off value for active intervention was identified to be at PLR >126.7. A longer duration of hospitalization was observed if the PLR exceeded the cutoff. Compared with non-severe cases, higher PLR was found in severe patients [34]. Bastug et al. [35], in their retrospective study investigating 191 hospitalized patients, found that PLR had a cut-off value of over 175.78 and NE had a cut-off value of over 4.11 on admission. Wang et al. [1] determined the cut-off value of PLR to be 267.03. In our study, we found a cut-off value of ≥255.556 for PLR, indicating severe illness and the need for ICU care. In our study, PLT was highest in the service group and lowest in the HF group. On the other hand, MPV gradually increased from ambulatory group to service and ICU groups. PLR gradually increased from the ambulatory group to the service and ICU groups.

Compared with moderate patients, the morphological parameters (RDW-CV and RDW-SD) were found to be significantly higher in the severe group [36]. This may be caused by the bone marrow suppressing immune damage. Compensatory hyperplasia of the erythroid cell line is caused by the consistent increase of anemia. Immature red blood cells are released into the peripheral blood. RDW increased due to the activation of red blood cell apoptosis and peripheral phagocytosis. In our study, the RDW-CV and RDW-SD values were found to be lowest in the outpatient group.

In our study, the most predictive indexes were NLR, PLR, LCR, NMR, LMR, and NER. Significant differences were found between the outpatient and ward group and ICU group in terms of LCR (p<0.001). The highest was found in the ICU group, followed by

outpatient admission, and then in the service group. In line with our results, in a meta-analysis of Lagunas et al. [37], the LCR values were decreased significantly in severe cases. A meta-analysis of Chen et al. [38] showed that in COVID-19, NLR and PLR can be used as independent prognostic markers of disease severity.

As our study is cross-sectional, we used the values of patients obtained on admission, and this is the most important limitation of our study.

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