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A Descriptive Study of 76 Cases of patients with COVID-19 and Prediction of Severity

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Abstract— ***Aim of the work:*** to clinically describe patients with COVID-19 who presented to El-Minia university hospital screening triage and to Clarify the simplest way to predict the severity of COVID-19.
Patients and methods: the current study is a retrospective study on the clinical criteria and laboratory results including inflammatory and coagulation markera (NLR, LMR, CRP, ferritin and D-dimer) of 76 patients of COVID-19. The patients classified based on the severity into severe and non-severe group.
Results: the median age of studied patient was 47 years old of them 43 male and 33 female. The risk of severity increased with hypertension and chronic kidney disease. As regards laboratory results in WBCs, neutrophil percentage and count, NLR, ALT, AST, urea and creatinine Significantly increased also there was an increase in inflammatory markers as CRP, ferritin and D-dimer with decrease in Hb, lymphocytes percentage, monocytes percentage level in severe group comparing to non-severe group. By applying binary logistic regression analysis it was found that increase in WBCs, Neutrophil count, NLR, ALT, Urea, Creatinine, CRP, Ferritin and D-dimer increasing the progression and severity of COVID-19.
Conclusion: lymphopenia and NLR especially CRP, ferritin also, inflammatory markers, is an effective and reliable indicator of the severity and indication of hospitalization in COVID-19 patients.

Key words: COVID-19, NLR, MLR, lymphopenia

Introduction:

Starting from early December 2019, groups of cases of pneumonia of unknown etiology have been reported in Wuhan, China. Coronavirus Disease 2019 (COVID-19) is a recent form of respiratory disorder tha caused by SARS-CoV-2 **[1]**. COVID-19 virus has been identified by the World Health Organization (WHO) and consider it as pandemic infection **[2]**. Since its first emergence in Wuhan, China, more than 15 million cases and more than 80,000 of deaths have been reported globally due to COVID-19 **[2]**. Some patients (about 98%) presented with mild influenza-like illness and may be asymptomatic, and about 2% of patients presented with symptoms of severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), with 91% recovery rate and 9% mortality rate **[2]**.

Clinical criteria and laboratory biomarkers that predict the risk of mortality and severity of COVID-19 are important in these pandemic situations. The lymphocytic count has been a marker of interest, since the first descriptive study done in China as regard that infection **[3]**. It was reported that decrease in the lymphocytic count was associated with severity of COVID-19 **[4]**. Cytotoxic T lymphocytes and natural killer cells are important for the control

of viral infection. While the immunological system in the body fight SARS-CoV-2 by , it was reported that there is a functional exhaustion of antiviral lymphocytes **[5]**.

Patients and methods:

This study was an observational retrospective studybased on epidemiological, demographic, clinical, laboratory data of 76 confirmed cases with COVID-19 at the time of admission from El-minia university hospital screening triage after oropharyngeal swabs, COVID-19 was confirmed by real-time RT-PCR. The data obtained from the medical reports.

The severity of COVID was defined based on the criteria established by China's National Health Commission **(6)**: 1- Mild: minor symptoms only, without evidence for pneumonia by chest X-ray. 2- Moderate: Fever and respiratory symptoms are present, and there is evidence for pneumonia by chest X-ray, (both groups classified also as non-severe cases). 3- Severe: Defined by any of the following conditions. 1) Dyspnoea, respiratory rate ≥30 /min, 2) resting hypoxia SaO2 ≤93%, 3) PaO2/FiO2 ≤300 mmHg. 4. Critical. The presence of any of the following conditions. 1) Respiratory failure, require mechanical ventilation, 2) shock, 3) other acute organ failure. (Both groups classified also as a severe cases).

Statistical analysis:

The analysis of the data was performed using the IBM SPSS 20.0 statistical package software. Data were expressed as median, interquartile range (IQR), mean and standard deviation (SD) for quantitative data, in addition to both number and percentage for categorized data. The Mann-Whitney test was used for comparison between two independent groups for non-parametric data, and the *Chi-square test or Fisher's exact test* was used to compare categorical variables. Predictive accuracy was measured by calculating the area under the receiver operating characteristic (ROC) curve. A binary logistic regression model was used to evaluate the predictive value of the different variables, using severity as the outcome. A *p*-value of 0.05 or less was considered significant, whereas values 0.01 and 0.001 were considered highly significant.

Results:

Table (1): Cases classification:

Mild	**36**	**(47.4%)**
Moderate	26	(34.2%)
Sever	7	(9.2%)
Critical	7	(9.2%)
Severity		
Non-severe	62	(81.6%)
Severe	14	(18.4%)

Table (2): Demographic characteristics among the severe and non-severe groups and their statistical significance:

	Non-severe (N=62)	Severe (N=14)	p value
Age			
Median (IQR)	47 (39-58)	65 (47-67)	**0.04***
Mean±SD	48±13	55±18	
Sex			
Male	34 (55%)	9 (64%)	0.519
Female	28 (45%)	5 (36%)	
Comorbidities			
Smoking	18 (29%)	4 (28.6%)	1.00
Hypertension	13 (21%)	7 (50%)	**0.042***
Diabetes	8 (13%)	4 (28.6%)	0.217
Chronic kidney disease	2 (3%)	5 (35.7%)	**0.002***
OTHERS	6 (10%)	1 (7%)	1.00

Table (3): clinical characteristics among the severe and non-severe groups and their statistical significance:

	Total (N=76)	Non-severe (N=62)	Severe (N=14)	p value
Temperature				
Median (IQR)	38.4 (38-38.8)	38 (38-39)	38.5 (38-38.7)	0.363
Mean±SD	38.3±0.6	38.3±0.6	38.5±0.4	
Respiratory rate				
Median (IQR)	21 (20-25)	20 (18-24)	35 (22-40)	**<0.001***
Mean±SD	23.3±7.6	21.1±4.4	32.9±11.1	
systolic BP				
Median (IQR)	110 (100-130)	110 (100-130)	125 (100-140)	0.426
Mean±SD	115.2±17.3	114.4±16.2	118.6±22.1	
diastolic BP				
Median (IQR)	70 (60-80)	70 (60-80)	80 (70-90)	0.241
Mean±SD	72.6±11.6	72±10.9	75±14.5	

Pulse *Median (IQR)* *Mean±SD*	100 (90-110) 99.5±11	95 (90-105) 97.7±10.1	109 (100-115) 107.7±11.5	**0.005***
O2 saturation *Median (IQR)* *Mean±SD*	96 (90-97) 91±13	96 (95-98) 96±3	78 (50-80) 68±17	**<0.001***

Table (4): Results of Laboratory investigations of the cases study and their statistical significance.

	Total	**Non-severe**	**Severe**	**p value**
	(N=76)	**(N=62)**	**(N=14)**	
Hemoglobin level *Median (IQR)* *Mean±SD*	12.6 (10.6-13.8) 12.1±2.2	12.8 (11.3-13.9) 12.4±2.1	10.6 (9-12) 10.7±2.2	**0.012***
Platelets *Median (IQR)* *Mean±SD*	233.5 (181-305) 252.9±93.9	246 (200-305) 262.3±92	181 (152-264) 211.1±93.7	0.05
Leucocytes *Median (IQR)* *Mean±SD*	6.4 (4.7-10.2) 8.4±5.4	5.9 (4.5-9.9) 7.4±4.1	10 (7.9-20.3) 12.7±8.1	**0.011***
Lymphocytes percentage *Median (IQR)* *Mean±SD*	23.5 (15.5-31) 24.2±11.9	26 (19-35) 26±11.5	15 (8.8-20.4) 16.6±11.1	**0.003***
Lymphocytes count *Median (IQR)* *Mean±SD*	1507.5 (970.5-2234.5) 1712.8±1055	1539.5 (968-2260) 1685±836.3	1383.5 (1000-1710) 1835.9±1766.2	0.625
Lymphocytes <1100	21 (27.6%)	18 (29.0%)	3 (21.4%)	0.745
Lymphocytes <1500	39 (51.3%)	31 (50.0%)	8 (57.1%)	0.629
Neutrophil % *Median (IQR)* *Mean±SD*	61 (55-69) 62±11.4	59.5 (54-65) 58.8±9.1	76.5 (70-84) 76.4±10	**<0.001***
Neutrophil Count *Median (IQR)* *Mean±SD*	3727 (2800-7320) 5441.8±4499.1	3484 (2440-5630) 4385.5±2767.8	7688 (6636-12400) 10119.5±7207.5	**0.001***
Monocytes % *Median (IQR)* *Mean±SD*	5 (4-6) 5.1±2	5 (4-6) 5.4±1.9	3 (3-4) 3.8±1.7	**0.002***
Monocytes Count *Median (IQR)* *Mean±SD*	320.5 (233.5-480) 381.6±217.1	313.5 (234-480) 378.8±219.3	358 (233-416) 393.9±214.9	0.625

NLR				**<0.001***
Median (IQR)	2.56 (1.71-4.16)	2.31 (1.64-3.21)	5.4 (3.25-9.55)	
Mean±SD	3.71±3.07	3.01±2.28	6.82±4.13	
LMR				0.315
Median (IQR)	4.75 (3.03-6.58)	4.9 (3.33-7.02)	4.1 (2.93-5.75)	
Mean±SD	5.28±3.01	5.33±2.72	5.08±4.19	
ALT				**0.04***
Median (IQR)	27.5 (19.5-40)	26 (18-36)	37 (22-55)	
Mean±SD	31.7±17.4	29.7±16.1	40.7±20.9	
AST				**0.033***
Median (IQR)	28 (18-38)	24.5 (18-33)	38 (24-45)	
Mean±SD	31±20.6	28.6±17	41.6±30.6	
Urea				0.004*
Median (IQR)	33 (26-41.5)	30 (22-40)	52.5 (33-110)	
Mean±SD	45.7±43.7	38.5±34.7	77.8±63.2	
Creatinine level				0.001*
Median (IQR)	0.9 (0.7-1.1)	0.9 (0.7-1)	1.5 (1-6)	
Mean±SD	1.4±1.8	1±1.1	3.2±3	
CRP				0.003*
Median (IQR)	15 (4.5-24)	12 (0-24)	23 (18-78)	
Mean±SD	22.4±29.7	16.8±18.5	47.5±51.4	
Ferritin				**0.001***
Median (IQR)	230 (99-465)	173 (87-353)	477.5 (331-877)	
Mean±SD	305.4±268.1	244.2±181.1	576.7±404.5	
D-dimer				**0.001***
Median (IQR)	0.8 (0.5-1.5)	0.70 (0.4-1.2)	2.5 (0.95-3.2)	
Mean±SD	1.2±1.03	0.97±0.83	2.22±1.23	

NLR= neutrophil lymphocytes ratio, LMR= lymphocytes monocytes ratio, ALT=alanine transaminase, AST=aspartate transaminase, CRP= C-reactive protein.

Table (5): Radiological signs and its difference between both groups:

	Non-severe (N=62)		Severe (N=14)		p value
Chest x-ray					
Bilateral consolidation	10	(16 %)	12	(85.7%)	**<0.001***
Bilateral reticular pattern	39	(63%)	0	(0.0%)	
No abnormalities	7	(11.3%)	0	(0.0%)	
bilat. reticulation + consolidation	6	(9.6%)	2	(14.3%)	
Chest CT					
bilateral GG+ consolidation+ crazy paving>2 Zone	26	(41.9%)	14	(100.0%)	**<0.001***
bilat. GG > 2 Zone	32	(51.6%)	0	(0.0%)	
No abnormalities	4	(6.5%)	0	(0.0%)	

Table (6): Receiver operating characteristic (ROC) curve of hematological parameters in prediction of the COVID-19 severity:

	Cutoff	AUC	p value	Sensitivity	Specificity	PPV	NPV
Lymphocytes %	≤20.4	0.753	<0.001*	78.6%	66.1%	34.4%	93.2%
Lymphocytes count	≤1710	0.525	0.756	78.6%	40.3%	22.9%	89.3%
Neutrophils count	>6380	0.787	<0.001*	78.6%	79%	45.85	94.2%
Monocytes count	>340	0.542	0.625	64.3%	59.7%	26.5%	88.1%
NLR	>2.76	0.831	<0.001*	92.9%	66.1%	38.2%	97.6%
LMR	≤4.5	0.586	0.307	64.3%	58.1*	25.7%	87.8%
Ferritin	>320	0.778	<0.001*	78.6%	72.6%	39.3%	93.7%
D dimer	>1.4	0.785	<0.001*	71.4%	78.9%	50%	92.9%
CRP	> 14	0.752	<0.001*	93%	58%	33.3%	97.3%

NLR= neutrophil lymphocytes ratio, LMR= lymphocytes monocytes ratio, CRP= C-reactive protein.

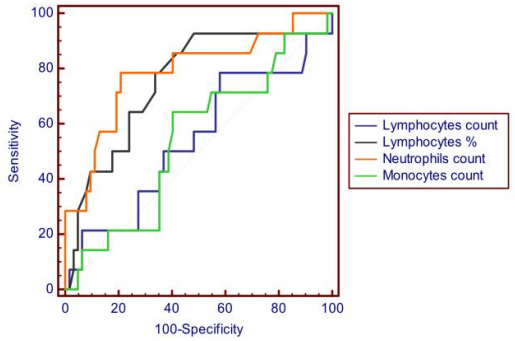

Figure (1)

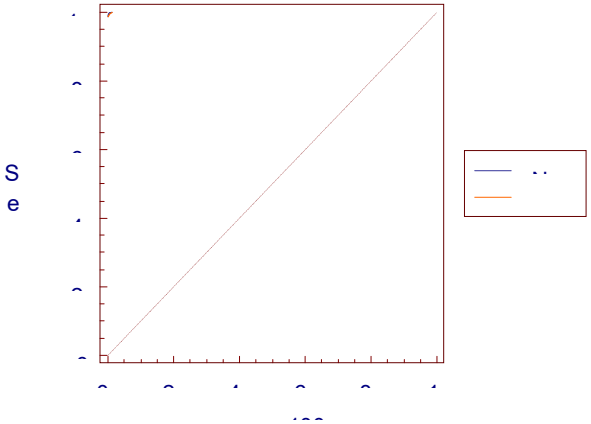

Figure (2):NLR= neutrophil lymphocytes ratio, LMR= lymphocytes monocytes ratio.

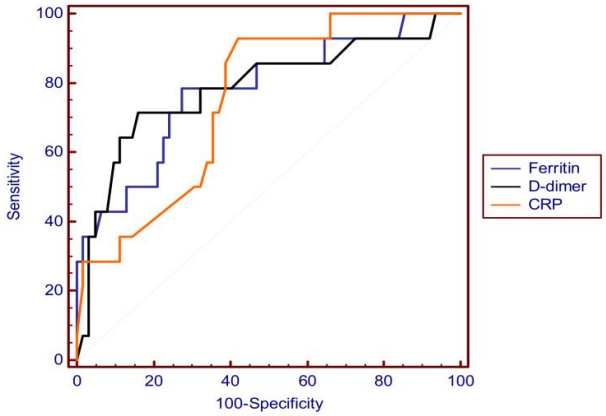

Figure (3): CRP= C-reactive protein.

Table (7): Odds ratio for factors affecting the severity:

	Univariate			Multivariate		
	COR	(95% CI)	p value	AOR	(95% CI)	p value

Age	1.04	(0.99-1.08)	0.117		
HB	0.71	(0.54-0.94)	**0.015****		
Leucocytes	1.17	(1.05-1.31)	**0.004***		
Lymphocytes%	0.92	(0.86-0.98)	**0.011***	0.96 (0.76-1.20)	0.701
Lymphocytes count	1.00	(1.00-1.00)	0.629		
Neutrophil count	1.00	(1.00-1.00)	**0.002***		
Monocytes count	1.00	(1.00-1.00)	0.813		
NLR	1.42	(1.17-1.73)	**<0.001***	1.45 (0.78-2.69)	0.24
LMR	0.97	(0.79-1.19)	0.78		
ALT	1.03	(1.00-1.06)	**0.045***		
AST	1.03	(1.00-1.05)	0.063		
Urea	1.02	(1.00-1.03)	**0.016***		
Creatinine	1.68	(1.19-2.38)	**0.004***	2.09 (1.19-3.66)	**0.010***
CRP	1.03	(1.01-1.06)	**0.007***	1.05 (1.01-1.09)	**0.014***
Ferritin	1.01	(1.00-1.01)	**0.001***	1.01 (1.00-1.01)	**0.032***
D-dimer	2.89	(1.61-5.18)	**<0.001***	0.95 (0.36-2.47)	0.911

NLR= neutrophil lymphocytes ratio, LMR= lymphocytes monocytes ratio, ALT=alanine transaminase, AST=aspartate transaminase, CRP= C-reactive protein.

Results:

In the present study It was reported about 76 cases that were confirmed to have SARS COV2 and classified based on severity (table 1), it was found that about 47% of patients presented with mild symptoms, 34% presented with moderate symptoms with evidence of pneumonia, while 9% for patients presented with severe to critical state and required intermediate unite and intensive care unit admission.As regard the Demographic data of the involved cases in it was shown that (table 2), there is statistical significance (P value 0.04) in the proportion of age in the group presented with sever symptoms with average age about 65 (55±18) in comparing to non-severe group 47 (48±13) years old. As regard sex The cases were 43 male and 33 female with no statistical significance. The risk of severity increased in the cases with hypertension (P value 0.042) and chronic kidney disease (P value 0.002).

In the current study there was (table 3); and statistical significant increase in respiratory rate (P value <0.001) and heart rate (P value 0.005) and statistical significance decrease in oxygen saturation (P value <0.001) in severe group in comparison to non-severe.
Regarding the laboratory findings at the time of screening (table 4); it was found that there was a statistical significance increase in number of WBCs (P value 0.011), neutrophil percentage and count (P value <0.001, 0.001 respectively), neutrophil lymphocytes ratio (NLR) (P value <0.001), ALT (P value 0.04), AST (P value 0.033), urea (P value 0.004) and creatinine (P value 0.001), this in association with increase in inflammatory markers as C-reactive protein (CRP), ferritin and D-dimer (P value 0.003, 0.001 and 0.001 respectively) together with reduction in Hemoglobin level (P value 0.012), percentage of lymphocytes (P value 0.003), monocytes percentage (P value 0.002) level in group presented with sever symptoms comparing to non-severe group. Following the study of the lymphocytes count and percentage; Lymphopenia was defined as a lymphocyte count of less than 1100 in these studies **(Liu et al., 2020 (7); Yang et al., 2020 (8); Zhang et al., 2020 (9))**, and as less than 1500 in one study **(Guan W-j et al., 2020) (10)**. Due to these variable reference regarding the level of lymphopenia it was used both references <1100 and <1500 to confirm occurance of the lymphopenia, it was found that on considering limit <1100 only 29% in non-severe group and only 21% in severe group was found to have lymphopenia. And by using the other reference <1500 to confirm presence of lymphopenia, it was found that 50% in non-severe group and 57% in severe group had lymphopenia. So the lymphopenia is a poor diagnostic marker. There was no statistical significance between both groups as regard the lymphocytes count (P value 0.773) with median range 1383.5 in severe group and 1504 in non-severe, monocytes count and lymphocytes monocytes ratio (LMR) had also no significant difference.

As regard the radiological investigation (table 5); in chest x-ray 63% of non-severe group had only reticular pattern with no evidence of pneumonia, while all patients in severe group has an evidence of pneumonia. In CT chest; in there was 51.6% has only ground glass appearance with no evidence of pneumonia and 41.9% had consolidation and about 6.5% looks normal in CT in the non sever group . Both of them had statistical significance (P value <0.001).
By application of ROC curve to define the optimal Cutoff point of markers that may used in predicting the severity (table 6); for lymphocyte percentage ≤20.4 has 78.6% sensitivity, 66% specificity, AUC 0.753 with P value <0.001 (figure 1).regarding neutrophil count the cutoff point was >6380 with 78.6% sensitivity, 79% specificity, AUC 0.787 with P value <0.001. NLR >2.79 had 92.9% sensitivity, 66% specificity, AUC 0.831 with P value <0.001 (figure 2). However regarding the lymphocytic count, monocyte count and LMR there was no statistical significance. The cutoff point for the CRP was > 14 had a sensitivity 93%, specificity 58%, AUC 0.752 and P value <0.001. Serum ferritin at cutoff point >320 had sensitivity 78.6%, specificity 72.6%, AUC 0.778 with P value <0.001. And for the D-dimer at cutoff >1.4 had a sensitivity 71.4%, specificity 78.9%, AUC 0.785 with P value <0.001(figure 3). In order To identify the markers that may affect the progression of COVID-19, we obtained the odds ratio (OR) after conducting the logistic regression analysis (table 7); increasing the level of WBCs, Neutrophil count, NLR, ALT, Urea and Creatinine increasing the progression with odds ratio of 1.17, 1.00, 1.42, 1.03, 1.02 and 1.68 respectively with P value 0.004, 0.002, <0.001, 0.045,0.016 and 0.004. While increasing the hemoglobin level and the lymphocytes% reduce the risk of severity and progression with odds ratio 0.71, 0.92 with P value 0.015 and 0.011.

While increasing other hematological markers such as CRP, ferritin and D-dimer lead to increasing the severity with odds ratio 1.03 ,1.01 and 2.89 respectively with P value 0.007, 0.001 and <0.001.

Discussion:

COVID-19 has evoked a rapid spread of outbreak with the human-to human transmission, with presentation of clusters of cases with atypical pneumonia. The demographic data of the current study showed older than what was found by**Yang, et al.** The average age in that case study was 58 years old and 42 years old for non-severe cases.The median age of severe patients was significantly higher than those presented with non-severe symptoms .There was no statistically significant difference between both groups was observed as regard gender.Also it was found that most severe cases reported associated co morbidities, with significantly high frequencies in the cases with diabetes ($p < 0.01$), hypertension ($p < 0.01$) and renal dysfunction ($p < 0.01$) **[11].** In other study, Patients age differed significantly between both groups (63.7 ± 16.8 for ICU vs 48.6 ± 15.6 for non-ICU patients) **[12].**

As regard the laboratory findings that was done to assess other organ function, the same results report that patients admitted to the ICU were more likely to had elevated AST (42.1% vs 14.8%), creatinine level (15.8% vs 4.1%) and blood urea nitrogen (26.3% vs 5.7%) as an indicator of renal dysfunction **[12]**.

On Studying the lymphocytes count and percentage The current study proved that there were wrong beliefs as regard this concept, and then we link the lymphopenia with degree of severity and progression of COVID-19.In comparison to **Liu et al., 2020 (7); Yang et al., 2020 (8); Zhang et al., 2020 (9)** and **Guan W-j et al., 2020 (10) that**reported that the presence of lymphopenia in its absolute count results in an approximately 3-fold increased risk of severity of COVID-19. Button a study done by**Zhang et al.**It's results were comparable today ours as regard the presence of lymphopenia in the percentages, but not in the absolute counts of lymphocytes, thatwas lower in severe patients when compared to non-severe patients. This may be explained by increase in the total numbers of leukocytes in severe patients **(13)in a study done by**. **Tan et al,** also stated that patients with LYM% > 20% were classified as moderate type and can recover quickly and Patients with LYM% < 20% were initially classified as severe type **[14]**.

lymhopenia would be explained by its role in maintaining immune homeostasis and inflammatory response in the body and persistence of lymphopenia in severe cases may be explained by direct viral infection of lymphocytes, as the lymphocytes has ACE2 receptors which had proved to be a target for COVID-19**(15)** or direct invasion of the virus to the lymphatic organs as thymus and spleen, this may lead to lymphocytic count decline. Presence of inflammatory cytokines leading to lymphocyte apoptosis **[16]**. Also leads to inhibition of lymphocytes by metabolic molecules, such as lactic acid which elevated in severe infections, might lead to suppression of lymphocytic proliferation [1**7].**

The results of the current study stated that elevated NLR was an independent prognostic factor that may help in prediction of pneumonia progression in COVID-19 patients.These findings were consistent with that of study done by **Yang, et al. [11]** who reported that age and NLR may be related to the severity of the infection and may also indicate the outcome of

the disease . There were many previous studies done to find the relationship between NLR and prognosis of many other infectious diseases [**19]**.

This neutrophilia may occur due to the fact that neutrophil (NEU) is a major component of leucocytes which release large amounts of reactive oxygen species that may induce cell DNA damage and release the virus from the cells. Leads to activation of cell mediated and humeral immunities. additional to production of numerous cytokines, such as circulating vascular endothelial growth factor (VEGF) that contributes to tissue inhibition and organ damage. Furthermore, NEU can be induced by virus-related inflammatory factors, such as interleukin-6 and interleukin-8, tumor necrosis factor-alpha and granulocyte colony stimulating factor, and interferon-gamma factors, produced by lymphocyte and endothelial cells **[20]**. On the other hand, systemic inflammation significantly caused depressesion of cellular immunity especially lymphocytes as mentioned before. Thus, virus-induced inflammation increased NLR and elevated NLR promote COVID-19 progression with occurrence of more severe clinical symptoms, and the progression from admission to ICU and mechanical ventilation was rapid **[21]**.

Several studies (Chang et al., 2020 **[22]**; Fang et al., 2020 **[23]**; Zhou et al., 2020 **[24]**) reported increased proinflammatory cytokines in serum of COVID-19 patients such as CRP and serum ferritin. Also, anti-inflammatory agents for COVID-19 therapy highlight the crucial role of inflammation in the progression of COVID-19 (Stebbing et al., 2020) **[25]**. These all studies reported that CRP level was positively correlated with the severity of COVID-19. Other previous studies that was done on SARS-CoV-2 showed a significant correlation between severity and prognostic outcome of COVID-19 in patients with increased D-Dimer levels **(26, 27)**.

Limitation:
sample size of our study is small. Single center experience.
we conclude that, lymphopenia and NLR is an effective and reliable biomarkersyhat help in predicting the severity and hospitalization in COVID-19 patients. In addition to , inflammatory markers, especially CRP, ferritin were positively correlated with the severity of COVID-19. Further studies are needed to find The association of serum ferritin with the severity of COVID-19 . Measuring inflammatory markers might help the clinicians in monitoring and evaluation of the severity and prognosis of COVID-19 and affect the treatment strategy.

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