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IL-6 level but not MBL level is associated with disease severity in hospitalized patients with COVID-19

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Abstract:

BACKGROUND AND AIM: The identification of reliable biomarkers for severe Coronavirus Disease 2019 (COVID-19) is still needed. Therefore, we analyzed mannose-binding lectin (MBL) in conjunction with interleukin-6 (IL-6) to elucidate their association with disease severity in COVID-19.

METHODS: In this prospective, observational cohort study, 88 patients with COVID-19 [severe (n=28), non-severe (n=60)] were analyzed. Correlations of serum MBL and IL-6 levels with laboratory parameters were analyzed. Receiver operating characteristic (ROC) curves were used to analyze the impact of MBL and IL-6 levels on disease severity. Logistic regression analysis (LRA) was performed to assess the association between severity and risk factors.

RESULTS: MBL level was similar in both groups (0.81 vs. 0.80 ng/mL, p=0.76) and showed no correlation between laboratory parameters nor hospitalization duration. The ROC curve showed that the area under the curve (AUC) of MBL was 0.520 (95% CI: 0.390-0.650, p=0.76). IL-6 levels were higher in the severe group (36.6 vs. 14.5 pg/mL, p=0.03) and correlated with hospitalization duration. At 32.75 pg/mL, IL-6 could differentiate the severe group with an AUC of 0.642 (95% CI: 0.512-0.771, p=0.03). In multivariate LRA, interleukin-6 level >32.75 pg/mL (Odds Ratio (OR): 3.991, 95% CI: 1.475–10.799, p=0.006) remained a significant risk factor for severe disease.

CONCLUSIONS: IL-6 has predictive value for both disease severity and hospitalization duration in COVID-19, while MBL is not a reliable biomarker for disease severity.

Keywords:

Complement system, coronavirus infection (COVID-19), disease severity, interleukin-6 (IL-6), lectin pathway, mannose-binding lectin (MBL)

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Introduction

Coronavirus Disease 2019 (COVID-19) is characterized by variable symptoms and prognosis among patients. The severity can range from asymptomatic infection to acute respiratory distress syndrome (ARDS) and even death. However, there are still many unanswered questions regarding which patients are at high risk of developing severe disease.[1,2] Therefore, the identification of reliable biomarkers of severe disease will contribute to the understanding of the pathophysiology of COVID-19 and likely serve as a guide for treatment strategies. Previously, a number of parameters such as lymphopenia, an increase in C-reactive protein (CRP), ferritin, or D-dimer have been found to be associated with the severity of COVID-19.[3] The relationship between Interleukin-6 (IL-6) and the inflammatory response in COVID-19 has also been extensively studied. IL-6 appears to be one of the most important mediators, and elevated IL-6 levels may predict disease severity in COVID-19.[4–6]

Moreover, systemic complement activation, which can be triggered via the classical pathway, the lectin pathway (LP), or the alternative pathway, has an established association with the manifestations of severe COVID-19 such as ARDS, sepsis, respiratory failure, and multiple organ failure (MOF).[7–10] However, few studies have focused on the complement system, particularly LP. Mannose-binding lectin (MBL), a pattern recognition molecule, can bind to microbial cell surfaces and activate LP.[11] As an opsonin, anti-antibody, and humoral factor, MBL also inhibits haemagglutination and infectivity to respiratory viruses.[12] There is also evidence that both genetic polymorphisms of MBL and its relationship to other components of the complement system play an important role in the dysregulation of the immune response caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[13] Based on the notion that MBL-deficiency patients are at high risk for SARS infection, MBL has been proposed to act as an immunomodulator against SARS-CoV-2.[12] However, it is not yet clear whether MBL levels can predict disease severity or prognosis. The aim of this study is therefore to clarify the value of MBL level in conjunction with interleukin-6 (IL-6) levels in predicting the clinical course of patients with COVID-19 and to better understand their relationships with clinical and laboratory findings.

Materials and Methods

Study design and study population

A prospective, single-institutional, observational cohort study was conducted in the COVID-19 ward of a tertiary hospital after ethical approval. Patients (≥18 years old) with confirmed COVID-19 [within 14 days of a positive polymerase chain reaction (PCR) for SARS-CoV-2] who were hospitalized in our institution 's COVID-19 wards between June 1 and August 8, 2021 (n=98) were selected for the study, and 94 out of 98 screened patients provided informed consent. Patients with documented concomitant infections (if detected), those who were transferred to another hospital, and those who were receiving tocilizumab (IL-6 receptor antagonist, Actemra, USA, Roche) or other immunosuppressive therapy prior to blood collection were excluded from the study. For the final analysis, the remaining 88 patients were included in the study [Fig. 1].

Patients were divided into two groups based on respiratory impairment and clinical management, and mortality during their hospitalization: severe COVID-19 and non-severe COVID-19. Patients were classified as severe COVID-19 based on one of the following criteria from the World Health Organization (WHO):[14] 1. requiring high-flow nasal cannula oxygen or non-invasive mechanical ventilation therapy, 2. undergoing endotracheal intubation and mechanical ventilation 3. requiring ventilation and additional organ support (vasopressors, extracorporeal membrane oxygenation (ECMO), etc.), 4. requiring intensive care unit (ICU) admission, or 5. dying due to COVID-19-related reasons during hospitalization. The remaining hospitalized patients were classified as non-severe COVID-19.

Patients' COVID-19-specific treatments were initiated in accordance with our local guidelines.[15] All decisions regarding patients' management were made by their primary clinicians, and there were no interventions by researchers.

Data collection

We obtained patients' data using the electronic medical record system of our hospital and Public Health Management Systems. We collected patients' demographic information (age, sex, and comorbidities), clinical, laboratory and radiologic findings. We recorder hospitalization duration, venous thromboembolic event (VTE) detection, and patient outcomes during hospitalization.

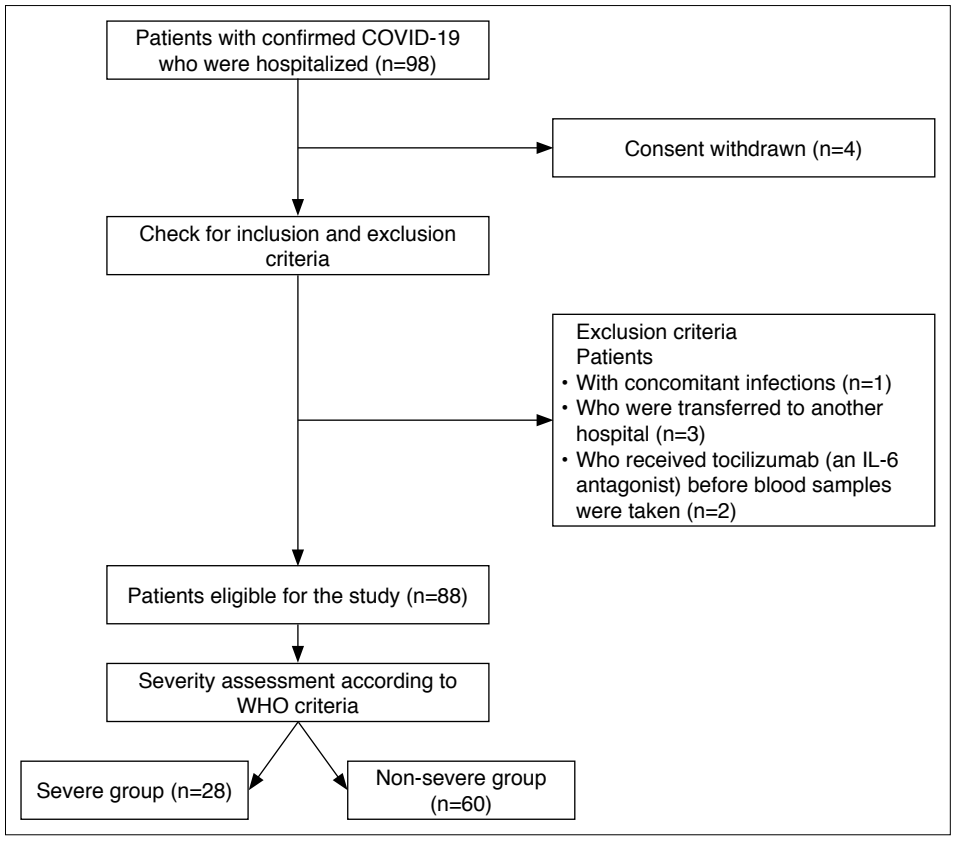

Figure 1: Flowchart of study population
WHO: World Health Organization

Ethics approval statement and patient consent statement

The study was approved by Keçiren Training and Research Hospital Clinical Research Ethics Committee with the number of 2012-KAEK-15/2316 (date: 25/05/2021) and was performed in accordance with the Good Clinical Practice guidelines and specific assent procedures for our country. We followed the Declaration of Helsinki and its subsequent revisions. Informed consents was obtained from the patient or next of kin if the patient was unable to provide consent.

Laboratory parameters and preparation of samples

We conducted routine laboratory tests for COVID-19 [(complete blood count, serum biochemistry, C-reactive protein (CRP), D-dimer, activated partial thromboplastin test (aPTT), prothrombin time (PT)-international normalised ratio (INR)] at our hospital and evaluated the results according to our hospital's normal laboratory values. All samples for MBL and IL-6 were collected within 24–48 hours of hospital admission. We immediately separated plasma samples after collection by centrifugation at 4000 rpm for 10 minutes at room temperature. We then stored them at –80°C in sterile test tubes and transported them on dry ice. We dissolved and stored them at 2–8°C for one day until analysis. The concentrations of MBL and IL-6 were measured using a specific enzyme-linked immunosorbent assay (ELISA) kit for MBL (Wuhan USCN Business Co., Ltd, China) (0.156–10 ng/mL) and a specific ELISA kit for IL-6 (DIA Source ImmunoAssays S.A.–Rue du Bosquet, 2-B-1348 Louvain-la-Neuve-Belgium) (1.5–7 pg/mL) in accordance with the manufacturer's instructions. We measured changes in absorbance to determine MBL and IL-6 levels. Analyses were performed by an experienced clinical microchemist who was blinded to the patients' characteristics.

Statistical analysis

Data analyses were conducted using IBM Corp. Released 2013 IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0. Armonk, NY: IBM Corp. Categorical data were described as the number of cases (%). Student's t-test was used to compare differences in normally distributed variables between two independent groups, and the Mann-Whitney U-test was used to compare non-normally distributed variables. Categorical

Table 1. Clinical features of the study population and comparison of patients according to disease severity

Variables	Total population (n=88)		Severe group (n=28, 31.8%)		Non-severe group (n=60, 68.2%)		p
	n	%	n	%	n	%	
Age, year	59.87±14.44		60.43±15.43		59.62±14.09		0.80
Sex							
Female	33	37.5	11	39.3	22	36.7	0.81
Male	55	62.5	17	60.7	38	63.3	
Comorbidity							
Yes	66	75	23	82.1	43	71.7	0.29
No	22	25	5	17.9	17	28.3	
Median hospitalization duration (median-IQR)	11 (8–15)		14 (11–23)		8.5 (7–12.5)		<0.001*
Venous thromboembolism	5	5.7	5	17,9	–	–	0.002*
Mortality in hospital	7	8	7	25,0	–	–	<0.001*
White blood cell (/mm^3) (mean±SD)	7570.2±3649.8		7747.5±3922.4		7487.5±3546.9		0.75
Thrombocyte (×10^3/mm^3) (mean±SD)	236.9±89.9		225.8±99.7		242.1±85.4		0.43
Lymphocyte (/mm^3) (median-IQR)	880 (550–1335)		720 (500–1045)		945 (660–1440)		0.03*
Lymphopenia (<800/mm^3)	39	44.3	16	57.1	23	38.3	0.09
C-reactive protein (mg/dL) (median-IQR)	76.5 (24–126.5)		98.5 (67.5–190)		59 (21–105.5)		0.003*
D-dimer (ng/mL) (median-IQR)	810 (500–1490)		800 (455–1280)		850 (505–1585)		0.41
D-dimer (≥500ng/mL)	64	72.7	19	67.9	45	75	0.48
Ferritin (ng/mL) (median-IQR)	394 (150.5–609.5)		467 (286–945.5)		287 (122.5–544)		0.03
aPTT (secs) (median-IQR)	25.3 (22.7–27.2)		25.5 (20.4–46.7)		25.3 (17.3–36)		0.80
INR (median-IQR)	1.13 (1.07–1.23)		1.19 (1.11–1.29)		1.11 (1.05–1.19)		0.01
Lactate dehydrogenase (U/L) (median-IQR)	281 (232–373.5)		310.5 (228.5–442.5)		275.5 (234.5–368)		0.48
Lactate dehydrogenase (≥248U/L)	57	64.8	17	60.7	40	66.7	0.58
Troponin (ng/mL) (median-IQR)	4 (2.25–12.5)		9 (4–14)		3 (2–11.5)		0.03*
Mannose-binding lectin (ng/mL) (median-IQR)	0.80 (0.53–1.32)		0.81 (0.54–1.29)		0.80 (0.53–1.34)		0.76
Interleukin-6 (pg/mL) (median-IQR)	15.64 (8.07–44.24)		36.65 (10.76–100.74)		14.53 (7.89–33.19)		0.03*

*: Statistically significant. Continuous data were described as mean±SD for normal distributions and median (interquartile range-IQR) for skewed distribution. Categorical variables expressed as frequency (percentage). Continuous variables were compared with Student t-test, and categorical variables were compared using the Chi-square test or Fisher exact test. IQR: Interquartile range, SD: Standard deviation, aPTT: Activated partial thromboplastin test, INR: International normalised ratio

variables were compared using Pearson's chi-square test or Fisher's exact test. The normality of continuous variables' distribution was analyzed with the Kolmogorov-Smirnov test. Levene's test was used to assess the homogeneity of variances. Unless otherwise stated, continuous data were presented as mean±standard deviation (SD) for normal distributions and median (interquartile range - IQR) for skewed distributions. Receiver operating characteristic (ROC) curves were used to analyze the impact of MBL and IL-6 values on disease severity. The Youden index was performed to determine the best cut-off values. Sensitivity and specificity were calculated for the cut-off values. The degree of relationship between variables was assessed using Spearman correlation analysis. In all statistical analyses, a p-value <0.05 was accepted as a significant level. Univariate logistic regression analysis was performed to assess the association between severity and risk factors. Multivariate logistic regression analysis was performed using the enter method for the variables with a univariate p-value <0.25.

Results

Results of clinical characteristics and laboratory markers in patients with COVID-19

A total of 88 patients who met the inclusion criteria were included in the study (Table 1). The mean age was 59.8±14.4 years at the time of diagnosis. Fifty-five (62.5%) patients were male and 33 (37.5%) patients were female. Sixty-six (75%) patients had at least one comorbid disease. The median hospitalization duration was 11 (8–15) days. A symptomatic Venous Thromboembolism (VTE) event was detected in 5 (5.7%) patients during hospitalization. Nearly 8% of patients (n=7) died in the hospital. Regarding laboratory tests, patients had a median lymphocyte count of 880 (550–1335)/mm^3, a median CRP level of 76.5 (24–126.6)/mg/dL, a median D-dimer level of 810 (500–1490)/ng/mL, a median ferritin level of 394 (150.5–609.5)/ng/mL, and a median troponin level of 4 (1–595)/ng/mL.

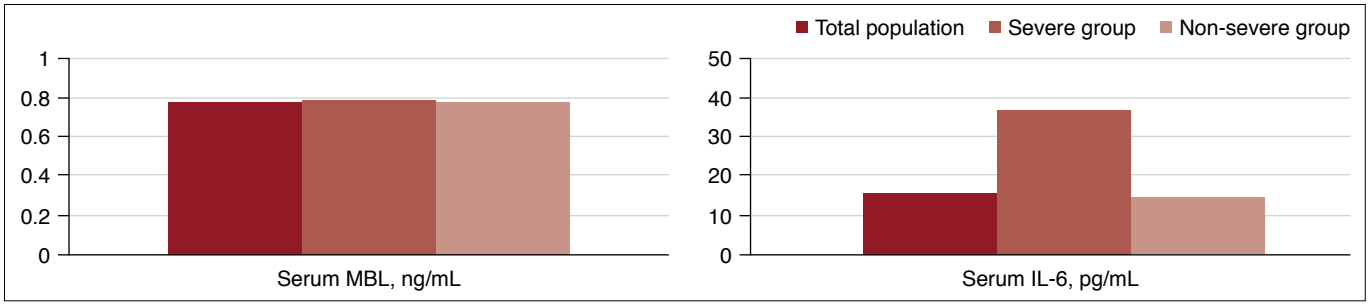

Figure 2: Serum mannose-binding lectin (MBL) and interleukin-6 (IL-6) levels in the total population, severe group, and non-severe group

According to the severity of COVID-19, patients were divided into severe (n=28, 31.8%) and non-severe (n=60, 68.2%) using the WHO criteria. When comparing the two groups, there were no significant differences in demographic characteristics such as age, sex, and presence of comorbidities (p=0.8, 0.81 and 0.29, respectively). VTE was only detected in the severe group. The median hospitalization duration of the severe group was significantly longer than that of the non-severe group (14 vs. 8.5 days, p<0.001). The lymphocyte count was significantly lower in the severe group (720/mm^3 vs. 945/mm^3, p=0.03). Laboratory tests were significantly higher for CRP (98.5 mg/dL vs. 59 mg/dL, p=0.003) and ferritin (467 ng/mL vs. 287 ng/mL, p=0.03), as well as troponin (9 ng/mL vs. 3 ng/mL, p=0.03) in the severe group. White blood cell, thrombocyte, D-dimer, aPTT, and Lactate Dehydrogenase (LDH) levels did not differ between the two groups (p=0.75, 0.43, 0.41, 0.8, and 0.48, respectively). The level of IL-6 was significantly higher in the severe group than in the non-severe group (36.6 pg/mL vs. 14.5 pg/mL, p=0.03). Conversely, the MBL level was similar in both groups (0.81 ng/mL vs. 0.80 ng/mL, p=0.76) [Fig. 2].

Correlations between MBL/IL-6 levels and laboratory markers and hospitalization duration in patients with COVID-19

There was no correlation between MBL level and IL-6 level (r=0.104, p=0.334). MBL level did not correlate with laboratory markers of thrombosis (D-dimer), markers of cardiac (troponin), or inflammatory markers (CRP or ferritin). IL-6, which is an inflammatory marker, was not correlated with CRP and ferritin. There was a weak but significant correlation between IL-6 and troponin (r=0.256, p=0.016). In addition, IL-6 showed a weak but significant correlation with the median hospitalization duration, while MBL did not correlate with the median hospitalization duration (r=0.228, p=0.032 and r =–0.124, p=0.252, respectively) (Table 2).

Use of the optimum cut-off values of MBL and IL-6 to distinguish severe from non-severe COVID-19

The result of ROC curve analysis showed that the area under the curves (AUC) of MBL was 0.520 (95% Cl: 0.390–0.650, p=0.76). At a cut-off value of 32.75 pg/mL, IL-6 was able to discriminate the severe group from the non-severe group with a sensitivity of 60.7% and a specificity of 75%, with an AUC of 0.642 (95% Cl: 0.512–0.771, p=0.03) [Fig. 3].

Results of the univariate and multivariate logistic regression analyses of predictive factors for severe COVID-19

Univariate logistic regression analysis showed that lymphocytes (Odds Ratio (OR): 0.999, 95% Cl: 0.998 – 1.000, p=0.04), ferritin (OR: 1.001, 95% Cl: 1.000–1.002, p=0.05), and the cut-off value of IL-6 (32.75 pg/mL) (OR: 4.636, 95% Cl: 1.780–12.078, p=0.002) were predictive factors for severe COVID-19. After the following multivariate analysis, only IL-6 level >32.75 pg/mL (OR: 3.991, 95% Cl: 1.475–10.799, p=0.006) remained significant as a risk factor for severe disease (Table 3).

Discussion

The results of the present study indicate that the IL-6 level was elevated in the severe group. A cut-off value of 32.75 pg/mL for IL-6 was able to distinguish severe COVID-19 from non-severe COVID-19, and patients with an IL-6 level higher than 32.75 pg/mL had an approximately 4-fold increased risk of severe disease. The utility of IL-6 as a reliable biomarker for identifying COVID-19 patients at higher risk of severe disease is underscored by these findings. However, MBL did not appear to be a useful biomarker for predicting the clinical severity of COVID-19. Furthermore, MBL levels did not show correlations with IL-6 or with other laboratory parameters, including markers of inflammation, thrombosis, or cardiac function.

Table 2. Correlation analyses between mannose-binding lectin (MBL)/interleukin-6 (IL 6) and blood markers/median hospitalization duration

Variable	MBL (ng/mL)		IL-6 (pg/mL)	
	Spearman's r	p	Spearman's r	p
Leukocyte (/mm³)	0.02	0.808	–0.024	0.826
Thrombocyte (×10³ /mm³)	0.118	0.272	–0.191	0.075
Lymphocyte (/mm³)	0.125	0.246	–0.157	0.143
C-Reactive protein (mg/dL)	–0.084	0.437	0.127	0.239
D-dimer (ng/mL)	–0.132	0.218	0.083	0.441
Ferritin (ng/mL)	–0.017	0.876	0.142	0.186
aPTT (secs)	–0.032	0.769	0.208	0.052
INR	–0.112	0.299	0.121	0.262
Lactate dehydrogenase (U/L)	–0.065	0.548	0.139	0.197
Troponin (ng/mL)	–0.111	0.305	0.256	0.016*
Hospitalisation duration (day)	–0.124	0.252	0.228	0.032*
IL-6 (pg/mL)	0.104	0.334		

*: Statistically significant. MBL: Mannose-binding lectin, IL-6: Interleukin-6, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

There is ample evidence that COVID-19 leads to cytokine storm syndrome (CSS) in 15–20% of patients, causing ARDS or MOF.[1,13] CSS is known to involve abnormal reactivity of the innate immune system, an unregulated inflammatory response, and excessive release of pro-inflammatory cytokines.[3,13,16] IL-6 plays a crucial role in this process by triggering acute phase responses, hematopoiesis, and immune reactions. In addition, downregulation of human leukocyte antigen DR isotype (HLA-DR) and lymphopenia are the result of the contribution of IL-6 to the persistent cytokine levels observed in severe COVID-19.[6,13,17,18] As shown in a meta-analysis of 16 studies, elevated IL-6 levels were consistently associated with the severity of COVID-19.[19] This association is in good agreement with recent studies and also confirms our findings.[18,20] Previous studies have also reported that different cut-off levels of serum IL-6 indicate clinical significance/outcomes. Jørgensen et al. and Herold et al.[17,21] found cut-off values for predicting respiratory failure of 10 pg/mL and 80 pg/mL, respectively. A meta-analysis by Aziz et al.[22] found a cut-off level of 55 pg/mL for detecting patients at high risk of severe disease. Another meta-analysis by Coomes et al.[16] also found an elevated IL-6 level was strongly associated with an increased risk of severe disease and was increased 2.9-fold in patients with complicated COVID-19 compared to patients with non-complicated disease. Consistent with these studies, we have shown that patients with IL-6 levels higher than 32.75 pg/mL have an approximately 4-fold increased risk of severe disease. Tocilizumab blocks the IL-6 signal transduction pathway and reduces the pro-inflammatory effect of IL-6.[23] As a monoclonal antibody of IL-6 receptor (anti-IL-6R), it has been used in COVID-19 patients with high IL-6 levels. Some studies have also shown that IL-6 blockade with tocilizumab was associated with a reduced need for mechanical ventilation and mortality, as well as improvements in respiratory and hemodynamic parameters.[24,25] However, some studies have contradicted these

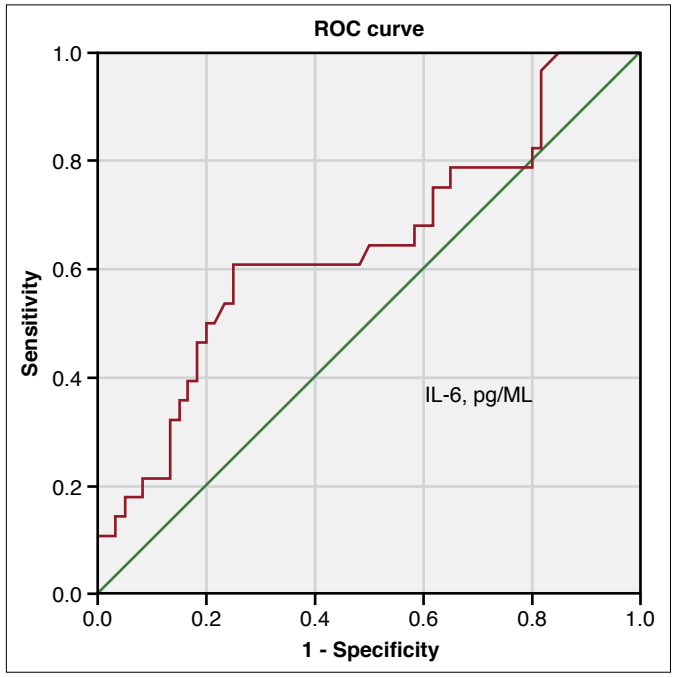

Figure 3: Receiver operating characteristic (ROC) curve analyses of interleukin-6 (IL-6) to predict disease severity in patients with COVID-19
The area under the curve for IL-6 is 0.642. The optimal cut-off value for IL-6 (the highest Youden's Index) is 32.75 pg/mL with a sensitivity of 60.7% and a specificity of 75%

Table 3. Results of univariate and multivariate logistic analyses of predictive factors for severe COVID-19

	Univariate logistic regression				Multivariate logistic regression			
	Wald	p	OR	95%CI for OR	Wald	p	OR	95%CI for OR
Age	0.061	0.80	1.004	(0.973–1.036)				
Sex (ref: female)	0.056	0.81	0.895	(0.356–2.251)				
Comorbidities	1.099	0.29	1.819	(0.594–5.564)				
Lymphocytes	3.901	0.04*	0.999	(0.998–1.000)	3.255	0.07	0.999	(0.998–1.000)
Thrombocyte	0.632	0.42	0.998	(0.993–1.003)				
C-reactive protein	0.973	0.32	1.008	(0.992–1.024)				
Lactate dehydrogenase	0.456	0.49	1.001	(0.998–1.003)				
D - dimer	1.303	0.25	1.000	(0.999–1.000)				
INR	0.685	0.40	1.407	(0.627	–3.160)			
Troponin	0.451	0.50	0.995	(0.981–1.009)				
Ferritin	3.714	0.05*	1.001	(1.000–1.002)	3.010	0.08	1.001	(1.000–1.002)
IL-6 (cut off 32.75)	9.861	0.002*	4.636	(1.780–12.078)	7.429	0.006*	3.991	(1.475–10.799)
MBL	0.090	0.76	1,129	(0.512–2.487)				

*: Statistically significant. Wald: Test statistics, OR: Odds radio, CI: Confidence interval, INR: International normalized ratio, IL-6: Interleukin-6, MBL: Mannose-binding lectin

results, so the use of tocilizumab in COVID-19 patients is still controversial.[5,23,26] We cannot comment on the effect of this agent because there were no patients using anti-IL-6R in our study. Furthermore, Taher Al Barzin et al.[27] showed that patients who were hospitalized for more than a week had higher serum IL-6 levels. Similarly, we have demonstrated that IL-6 level has a weak but positive correlation with the length of hospital stay. The results of our study support the role of IL-6 in the pathogenesis of COVID-19 and provide additional evidence for the usefulness of IL-6 as a dependable biomarker in predicting severe COVID-19 and the length of hospitalization.

In addition to the overexpression of proinflammatory cytokines and chemokines, known as ''CSS'', several mechanisms, such as the complement system, may be involved in the pathogenesis of COVID-19.[8] LP, which has multiple pattern recognition receptors such as MBL, collectins, and ficolins, is probably the first line of host defense to get activated after infection with SARS-CoV-2 by MBL - MBL associated serine protease complex.[7,28,29] This complex can promote complement activation by cleaving C3 and is also involved in neutralizing the virus, clearance, and promoting inflammation.[7] Serum MBL levels peak within 5 days of birth and then begin to decline with age.[29] Normal values vary from very low levels to 10 ng/mL.[13] The study by Zogheib et al.[30] of critically ill patients with H1N1 infection found higher MBL levels in non-survivors compared to survivors and the control group. Although our study did not include a control group consisting of healthy individuals, the MBL level in each patient was within normal limits (0.33–2.46 ng/mL). The fact that the MBL level was normal while IL-6 increased in our study population is consistent with the idea that the marker associated with the complement cascade may not be useful in routine clinical practice because it is unstable and has a short half-life.[31] Moreover, MBL as an Acute Phase Response (APR) shows a high degree of heterogeneity in different infections.[32,33] Wang et al.[11] showed that MBL suppresses the production of peptidoglycan-induced inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and IL-6 through different pathways and thus could function as an APR. The study by Holter et al.[10] found that MBL levels in patients with COVID-19 were comparable to those in the normal population, with a limited increase on days 3 to 5, consistent with APR. However, our results are consistent with the findings of Erikkson et al.[34] that MBL levels do not correlate with IL-6, CRP, and ferritin, suggesting that MBL is not a typical APR. The differences between the studies seem to suggest that MBL has different effects in different circumstances and at different stages of acute illness.[35]

Different results have also been published on the relationship of MBL and disease severity and mortality in patients with COVID-19. For example, extensive deposition of MBL was demonstrated in the postmortem lungs of COVID-19 patients with ARDS.[8,36] These results could mean that MBL deposition is one of the responsible factors for mortality from lung injury. Defendi et al.[37] also demonstrated an association between MBL pathway activation and mortality. In contrast to other studies, Eriksson et al. showed that MBL levels were not related to disease severity and mortality, and Sinkovits et al.[34,38] demonstrated that there were no differences between LP activity and severity groups. Our study came to a similar conclusion, suggest-

ing that measuring MBL levels is not suitable for distinguishing COVID-19 patients at high risk for severe disease.

Limitations

Our study has several limitations. The study population is relatively small as the study was conducted in a single center. We measured circulating serum MBL levels, but assessment of genotype and MBL activity may be necessary to gain comprehensive insight into complement activation at COVID-19. Finally, MBL is thought to be involved in the increase in coagulation during thromboinflammation in COVID-19 patients. We detected only 5 (5.7%) patients with confirmed Thromboembolism (TE). The lower incidence of TE events than expected is probably due to performing fewer radiological procedures in our center due to the risk of transmission, the poor performance status of patients, or treatment protocols such as non-invasive/invasive mechanical ventilation or the requirement of prone positioning. Another possible explanation is that we only evaluated venous TE complications and not arterial and venous TE complications.

Conclusion

Clinicians may be able to detect severe disease earlier, improving prognosis by understanding how biomarkers act in the progression of disease. Our study has shown that an elevated IL-6 level has the potential to identify COVID-19 patients at higher risk for severe outcome, whereas MBL level does not appear to be a useful biomarker for predicting the clinical severity of COVID-19. We believe there is a need for further research into the pathophysiological mechanism behind COVID-19, and our study will serve as a basis for future studies, especially on complement activation in COVID-19.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Ankara Keçiören Traininig and Research Hospital Clinical Research Ethics Committee (No: 2012-KAEK-15/2316, Date: 25/05/2021).

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Authorship Contributions

Concept – Y.S., P.A.K., D.K., M.B.B., Ü.Y.; Design – Y.S., P.A.K.; Supervision – Ü.Y., Y.S.; Materials – Y.S., P.A.K., D.K., A.T., M.B.B., Ü.Y.; Data collection &/or processing – Y.S.; Analysis and/or interpretation – Y.S., P.A.K., D.K., A.T., M.B.B., Ü.Y.; Literature search – Y.S., P.A.K., D.K., A.T., M.B.B., Ü.Y.; Writing – Y.S.; Critical review – Y.S., Ü.Y., P.A.K.

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