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ORIGINAL ARTICLE

A New Approach to Predicting Prognosis in SARS-CoV-2 Infection: "MELD Scoring"

SARS-CoV-2 Hastalarında Prognozun Öngörülmesine Yeni Bir Yaklaşım "MELD Skorlaması"

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ABSTRACT

Background/Aims: The MELD score is a scoring system used to assess the severity of end-stage liver disease. In our study, we aimed to investigate the role of MELD score in predicting the course of the disease and mortality in COVID-19 disease with multi-systemic involvement.
Methods: Our study was conducted with 96 patients over the age of 18 who were diagnosed with COVID-19 by real time PCR method by taking nasopharyngeal swabs between March 2021 and March 2022. MELD score was calculated according to the blood results of the patients at the time of hospital admission. To calculate the MELD score, the equation MELD = 11.2 x ln(international normalized ratio [INR]) + 3.78 x ln(bilirubin, mg/dL) + 9.57 x ln(creatinine, mg/dL) + 6.43 was used.
Results: We found that the MELD score was significantly higher in the moderate and severe patient group compared to the mild patient group ($p<0.01$). When we compared the moderate and severe patient groups between themselves, the MELD score was significantly higher in the severe patient group ($p<0.01$). In the evaluation of the association of MELD score with mortality, a one-unit increase in MELD score was associated with a 1.26-fold (95% confidence interval: 1.10-1.44) increased mortality risk.
Conclusions: In our study evaluating the MELD score in COVID-19 patients, it was observed that the MELD score during hospitalization was closely associated with disease severity and mortality. Therefore, the MELD score may be a guiding scoring system in the early follow-up of COVID-19 patients.

Keywords: MELD, COVID-19, Mortality

ÖZ

Amaç: MELD skoru, son dönem karaciğer hastalığının şiddetini değerlendirmek için kullanılan bir skorlama sistemidir. Çalışmamızda multisistem tutulumu olan COVID-19 hastalığında MELD skorunun hastalığın seyrini ve mortaliteyi tahmin etmedeki rolünü araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmamız Mart 2021 – Mart 2022 tarihleri arasında nazaofaringeal sürüntü alınarak real time PCR metoduyla COVİD-19 tanısı alan 18 yaş üstü 96 hasta ile yapılmıştır. MELD skoru hastaların hastaneye yatış anındaki kan sonuçlarına göre hesaplandı. MELD puanını hesaplamak için şu denklem kullanıldı: MELD = 11,2 x ln(uluslararası normalleştirilmiş oran [INR]) + 3,78 x ln(bilirubin, mg/dL olarak) + 9,57 x ln(kreatinin, mg/dL olarak) + 6,43.
Bulgular: MELD skorunun orta ve şiddetli hasta grubunda hafif hasta grubuna göre anlamlı olarak yüksek olduğunu bulduk ($p<0.01$). Orta ve ağır hasta gruplarını kendi aralarında karşılaştırdığımızda şiddetli hasta grubunda MELD skoru anlamlı olarak daha yüksekti ($p<0.01$).MELD skorunun mortalite ile ilişkisinin değerlendirilmesinde, MELD skorundaki bir birimlik artış, 1.26 kat (%95 güven aralığı: 1.10-1.44) artmış mortalite riski ile ilişkilendirildi.
Sonuç: COVID-19 hastalarında MELD skorunu değerlendiren çalışmamızda hastanede yatış sırasındaki MELD skorunun hastalık şiddeti ve mortalite ile yakından ilişkili olduğu gözlendi. Bu nedenle MELD skoru, COVID-19 hastalarının erken takibinde yol gösterici bir skorlama sistemi olabilir.

Anahtar Kelimeler: MELD, COVİD-19, Mortalite

Introduction

COVID 19, which was first seen in Wuhan, China in December 2019, soon affected the whole world and reached pandemic proportions. It has caused more than 6 million deaths worldwide. Due to the rapid spread and the high number of cases, there was an increase in patient hospitalization in hospitals and intensive care units (1).

In patients diagnosed with COVID 19; the course of the disease varies. The disease may start with symptoms of influenza infection and progress asymptomatically, or it may cause severe pneumonia, acute respiratory distress syndrome, multiple organ failure and death (1). A successful risk stratification system that will be useful in predicting the course of disease in COVID 19 patients based on this variable clinical presentation is needed to prevent unnecessary hospitalizations and reduce the burden on health systems worldwide. Studies have shown that age, gender and comorbidity-based systems are successful in predicting mortality (2). CRP, D-dimer, creatinine, ferritin, LDH, international normalized ratio (INR) levels, neutrophil/lymphocyte ratio and many other biomarkers have been evaluated to determine the level of weight and predict mortality in COVID-19 patients (3, 4). However, it has been observed that the combined use of these markers, which are insufficient in single evaluation, may give more favorable results in follow-ups about the course of the disease (5).

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The MELD (Model of End-Stage Liver Disease) score is a scoring system widely used to determine the severity of disease and predict short-term mortality in end-stage liver disease (6). MELD includes 3 commonly used laboratory variables including INR, serum creatinine and serum bilirubin. Although MELD scoring is generally used in liver transplantation to identify candidate recipients, a retrospective analysis of the MELD score in COVID-19 patients showed that it was closely associated with mortality and length of hospitalization (7-9). It has been stated in studies that the multi-systemic effects of SARS-CoV-2 virus, which has a high lung affinity, may be associated with high MELD score in these patients due to the liver damage it causes with the understanding of its multi-systemic effects in the later stages of the disease (8, 10).

In our study, unlike previous studies on MELD score, we aimed to determine the level of MELD score between patient groups in the early period and its relationship with mortality in follow-up.

Material and Method

Ethics Committee permission was obtained from local ethics committee with the decision dated 06.06.2022, numbered 2022/07-85. Patient information was obtained retrospectively from the hospital data processing system after the decision of the local ethics committee. Our study was conducted between March 2021 and March 2022 with 96 patients over the age of 18 who were diagnosed with COVID-19 confirmed by real time PCR method by taking nasopharyngeal swabs. The hospital records of the patients were carefully reviewed by the study team. Patient data including laboratory investigations, medical history, comorbid conditions, complications, demographics, initiated treatments and outcomes were collected and analyzed. MELD score was calculated according to the blood results of the patients at the time of hospital admission. The equation used to calculate the MELD score is as follows: MELD = 11.2 x ln (international normalized ratio [INR]) + 3.78 x ln (bilirubin, in mg/dL) + 9.57 x ln (creatinine, in mg/dL) + 6.43 (11).

The 96 patients included in our study were divided into 3 groups according to the severity of the disease. The classification of patients according to weight was performed according to the current Republic of Turkey Ministry of Health of Turkey COVID-19 adult diagnosis and treatment guideline published at the time of the study (12). Group 1 was named as the mildly severe disease group. Patients in this group consisted of patients with normal chest radiographs who were not hospitalized and were treated in outpatient clinics (n=32). Group 2 was termed as the moderately severe disease group. Patients in this group consisted of patients with clinical signs of pneumonia without signs of severe pneumonia and requiring hospitalization in clinics (n=32). Group 3 was named as the serious severe disease group. This group consisted of patients hospitalized with severe pneumonia who developed macrophage activation syndrome during follow-up and required intensive care unit hospitalization (n=32). Patients who met one of the following criteria: respiratory rate ≥ 30 breaths/min; SpO2 ≤ 92%; and lung infiltration rate >50% were considered to have severe pneumonia.

Patients with previously known or diagnosed chronic renal failure after hospitalization, chronic liver disease, and patients using oral anticoagulants, especially warfarin, which would affect the MELD score were excluded from our study. In addition, patients whose blood INR, bilirubin and creatinine values were not checked at hospital admission were excluded from the study.

When the hospital records of the patients included in our study were examined, COVID-19 treatment protocols were determined according to clinical severity as stated in the Turkish Ministry of Health COVID-19 adult diagnosis and treatment guidelines (12). Patients hospitalized with moderate COVID-19 were treated with dexamethasone 6 mg/day and nasal oxygen 2-4 l/min for 7 days. Favipiravir was administered as antiviral therapy at a loading dose of 2x 1600 mg and a maintenance dose of 2x 600 mg for 5 days. In addition to the treatment of patients hospitalized with moderate COVID-19 pneumonia, hospitalized patients with severe COVID-19 pneumonia were given oxygen therapy with a high-flow nasal cannula with SpO2 > 92%. After improvement in saturation levels in this patient group, 2-4 l/min nasal oxygen therapy was started. Patients who did not respond to oxygen therapy with high-flow nasal cannula were followed up with noninvasive or invasive mechanical ventilation according to treatment response and compliance.

Statistical analyses were performed using SPSS 25.0 package program (SPSS, Chicago). Normality of the data was checked by Kolmogorov-Smirnov test. Levene's test was used to evaluate the equality of variances. Mean±standard deviation was used for normally distributed data and median (minimum-maximum) was used for non-normally distributed data. Normally distributed parameters of the three groups were compared by One-Way ANOVA and post-hoc tests were used to determine pairwise differences between the groups (Tukey test when variances were equally distributed and Dunnett T3 test when variances were not equally distributed). Non-normally distributed parameters of the three groups were compared by Kruskal-Wallis test and Mann-Whitney U test was used to make pairwise comparisons when there was significance between the groups. Pearson chi-square test was used to compare the categorical variable gender. Binary logistic regression analysis was performed to examine the effect of MELD score on mortality. Receiver operating characteristic (ROC) analysis was performed to identify MELD score cut-off values that predict mortality.

Results

Demographic characteristics (age, gender) of the patients are shown in Table 1. The mean age of all COVID-19 patients (n=96) was 57.2±18.2 years. Statistical analysis showed that there was a significant

difference in terms of age in the mild, moderate and severe groups (p<0.01). In addition, there was no significant difference in terms of gender between the mild, moderate and severe groups. Laboratory data of the patients are shown in Table 2. INR and total bilirubin were significantly higher in the moderate and severe groups compared to the mild group. Lymphocyte percentage and count were significantly lower in the severely ill group compared to the other groups. Ferritin, lactate dehydrogenase (LDH), CRP and D-dimer were significantly higher in the severe group.

MELD scores of the patients are shown in Table 3 and Figure 1. Accordingly, MELD score was statistically higher in Group 3 patients compared to both Group 1 and Group 2 patients. In addition, MELD score was also statistically significantly higher in Group 2 patients compared to Group 1 patients (p<0.01 for all).

In our study, mortality was observed in 14 of the patients followed up. Of these patients, 12 were Group 3 patients and 2 were Group 2 patients. Binary logistic regression analysis was performed to examine the effect of MELD score on mortality. Mortality status was taken as the dependent variable and MELD score as the independent variable. When the regression summary was analyzed, it was seen that the independent variable MELD score could explain 86% of the variance in the dependent variable (mortality) and this value was significant (p<0.01). A one-unit increase in MELD score was associated with a 1.26-fold (95% confidence interval: 1.10-1.44) increased mortality risk (Table 4).

The results of receiver operating characteristic (ROC) curve analysis to predict mortality are as follows: Area under the ROC curve (AUC): 0.85 (95% confidence interval: 0.75-0.96) (P<0.01), the cut-off MELD score value was 13.5 (odds ratio-LR:3.36), predicting mortality with high sensitivity (80% sensitivity and 76.3% specificity). LR was small and cannot be used as a strong cut-off value. ROC analysis to predict mortality revealed that the MELD score was able to detect 85% of mortality (Figure 2).

Table 1. Demographic and clinical characteristics of the patients

	All Patients (n=96)	Mild (n=32)	Moderate (n=32)	Severe (n=32)
Age (years)	57.2±18.2**	43.9±16.5[a]	67.6±16.1	59.6±13.9[b]
Gender, M/F(%)	56/44	56/44	44/56	68/32

Age is represented as mean±standard deviation, M/F: male/female. Results are expressed as median (minimum-maximum); **: p<0.01 for one-way ANOVA test; a,b post-hoc Tukey test shows P values below 0.05 (a significant difference between mild and moderate patients; b significant difference between mild and severe patients)

Table 2. Results of biochemical parameters of the patients and comparisons between groups

	Groups				P
	All patients (n=96)	Mild (n=32)	Moderate (n=32)	Severe (n=32)	
INR	1.46±0.1	0.96±0.4[a]	1.43±0.9	1.51±0.7[b]	<0.01**
Total bilirubin, mg/dl	1.09±0.7	0.46±0.5[a]	1.36±0.1[c]	1.70±0.7[b]	<0.01**
Creatinine, mg/dl	1.22±0.9	0.82±0.1	1.16±0.6[c]	1.72±1.2[b]	0.010*
Neutrophil Percentage, %	78.6±22.4	69.1±12.7	78.4±18.9	89.1±19.3	0.257
Lymphocyte Percentage, %	15.4±12.06	27.6±9.3[a]	16.3±8.7[c]	11.1±5.6[b]	<0.01**
Neutrophil Count, /µl	8.2±5.4	5.1±1.6[a]	12.2±4.7[c]	15.3±7.2[b]	<0.01**
Lymphocyte Count, /µl	1.2±0.8	2.1±0.8[a]	1.2±0.7	0.8±0.5[b]	0.010*
Platelets, 10^3 µl	297.5±107.8	276.4±82.1[a]	281.6±131.2[c]	334.7±112.7[b]	<0.134
Ferritin, ng/m	485.7 (36-2950)	145 (36-920)[a]	643 (102-2950)	1430 (226-2890)[b]	<0.01**
CRP, mg/dl	81.3 (3-340)	41.5 (3-87)[a]	76.2 (9-290)	127.4 (11-340)[b]	<0.01**
LDH, U/L	368.6 (132-1226)	184.1 (132-295)[a]	405.8 (155-820)[c]	517.3 (215-1226)[b]	<0.01**
Fibrinogen, ng/m	341.3 (55-775)	356.3 (175-590)[a]	398.5 (191-651)[c]	270 (53-775)	0.024*
D-Dimer, ng/m	661.3 (190-35200)	275.3 (190-970)[a]	867.3 (346-35200)	842.1(440-35200)[b]	<0.01**

Results are expressed as mean±standard deviation for normally distributed data and median (minimum-maximum) for non-normally distributed data; P: One-way ANOVA test statistics P value for normally distributed data and Kruskal-Wallis test statistics P value for non-normally distributed data; * : p<0. 05, ** : p<0.01, a,b,c post-hoc Tukey test/Dunnett's T3 test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data) P values less than 0.05 (a significant difference between mild and moderate patients; b significant difference between mild and severe patients; c significant difference between moderate and severe patients)

Table 3. MELD scores of patients and comparisons between groups

	Groups				*P*
	All patients (n=96)	Mild (n=32)	Moderate (n=32)	Severe (n=32)	
MELD Score	11.6±5.4	6.7±0.7[a]	11.7±2.6[c]	16.2±5.8[b]	<0.01

Results are expressed as mean±standard deviation; P: One-way ANOVA test statistics P value; a,b,c post-hoc Tukey test indicates that P values are below 0.05 (a Significant difference between mild and moderate patients; b Significant difference between mild and severe patients; c Significant difference between moderate and severe patients)

Table 4. Results of binary regression analysis (dependent variable: mortality)

Independent Variable	B	SE	Wald	-2 Log Likelihood	Nagelkerke R square	Overall percentage	Odds Ratio	CI (Confidence Interval)	*P*
MELD Score	-2.0	0.33	11.46	47.3	0.315	86.0	1.26	1.10-1.44	<0.01

P: Test statistics P value

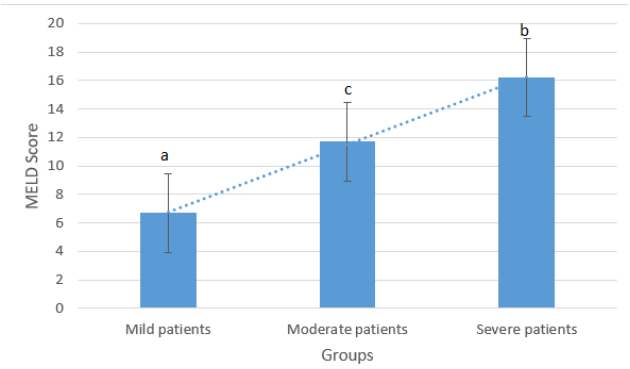

Figure 1. MELD scores of patients and comparisons between groups. a,b,c post-hoc Tukey test indicates that P values are below 0.05 (a Significant difference between mild and moderate patients; b Significant difference between mild and severe patients; c Significant difference between moderate and severe patients)

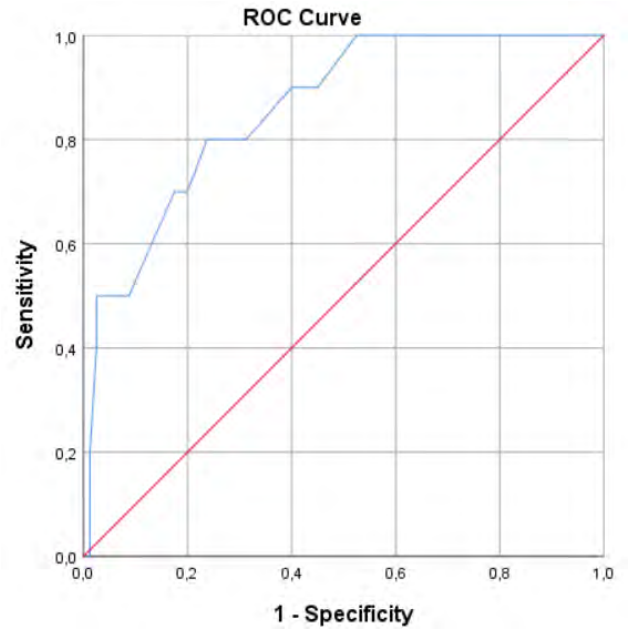

Figure 2. ROC curve for mortality status prediction with MELD score values

Discussion

In our study, it was observed that the MELD score at the time of hospital admission increased in correlation with the clinical course of the disease. In addition, it was observed that patients with mortality during follow-up had high baseline MELD scores. In the comparison of laboratory data and demographic characteristics, it was observed that age, LDH, ferritin, CRP and D-Dimer levels were higher in moderate-heavy patients compared to mild patients in accordance with the literature.

As a multi-systemic infection, COVID-19 can be asymptomatic or affect vital organs. In patients in whom vital organs are affected, intensive care hospitalization may be required and this process may result in mortality. Especially in some patient groups, damage to many vital organs, especially the lungs, may occur due to overproduction of proinflammatory cytokines (1).

The ability to assess organ dysfunction at the bedside can help optimize treatment and predict the prognosis of critically ill patients (13, 14). Various scoring systems can be used for this purpose. The MELD score is a scoring system used to predict survival in patients with end-stage liver disease to prioritize patients who are candidates for liver transplantation (7). The MELD score is calculated using serum creatinine, bilirubin and INR parameters. Serum bilirubin and INR levels indicate liver function, while creatinine levels indicate renal function (15). Studies have shown that the MELD score can also be used to predict mortality in patients without liver disease, especially in patients requiring intensive care hospitalization (9, 16, 17). There are also studies in the literature showing that it can be used for risk stratification in critically ill patients (18, 19).

After the SARS-CoV-2 virus, which has a high affinity for the upper and lower respiratory tract, enters the body, proinflammatory cytokine synthesis begins by many cells that play a role in immunity, especially macrophages. Among these cytokines, TNF-alpha, IL-1, IL-6 and IL-18 play an important role. Failure to adequately balance the intensely synthesized proinflammatory cytokine discharge with the anti-inflammatory response may lead to disease progression (20, 21). Cytokines synthesized during this period, described as a cytokine storm, cause endothelial dysfunction in many organs and tissues. In addition, in organs and tissues where the ACE2 receptor, which plays an important role in the binding of SARS-CoV-2 virus to the cell, the virus can directly increase damage (22). As the disease progresses, increasing studies have shown that the ACE2 receptor is also found in kidney, liver and bile duct epithelial cells in addition to the lungs. In addition to increased cytokine discharge, organ dysfunction as a result of direct damage caused by the virus causes liver and kidney function tests to deteriorate in patients (23).

Although the MELD score was first used to calculate life expectancy in people with chronic liver disease, the biochemical parameters used in its calculation have an important role in the prognosis and clinical course of many diseases, especially pulmonary thromboembolism and many infectious diseases (24-26). In study on MELD score in COVID-19 patients, it was observed that mortality was higher in patients with a score of 10 and above, that is, patients with a high MELD score, and that these patients had more days of hospitalization (8, 27). In the evaluation of the modified MELD-XI score in patients with moderate-high risk pulmonary thromboembolism, it was concluded that it may be an important scoring system in predicting mortality (28).

In our study, in accordance with previous literature studies on COVID-19 patients, it was observed that the clinic of the patients worsened in correlation with the increase in age (29). It was also observed that LDH, ferritin, CRP and D-Dimer levels were higher in patients presenting with a severe course compared to patients with a mild and moderate course. This may be attributed to direct or indirect endothelial damage

caused by COVID-19 by inducing proinflammatory cytokine discharge (30). In addition, ferritin (31), which is released as a result of direct stimulation of the heme oxygenase system by viral infections, may have been released more in patients with severe course due to intense viral load. Higher bilirubin and creatine levels in severe patients compared to mild and moderate patients, as well as higher INR levels compared to mild patients, caused the MELD score to be higher in severe patients. In this case, like other laboratory tests associated with mortality, it may have been observed due to direct damage caused by the virus to the liver, kidney and biliary system as well as intense synthesized proinflammatory cytokine discharge. Increasing MELD score in COVID-19 was an indirect finding indicating the severity of multi-systemic involvement. As a result, it was found that mortality was observed to be higher in patients with increasing MELD score. For chronic liver diseases, 10 points in the MELD score was used as low and high scoring (8). However, in our study, we observed that the sensitivity and specificity of 13.5 points were higher in predicting mortality in COVID-19 patients.

In our study in which the relationship between MELD score and clinical severity was evaluated, our most important limitation was that the change in MELD score could not be monitored during follow-up. The guidelines set by the Ministry of Health were applied in the follow-up of the patients. In line with the guideline, the follow-up MELD score was not included in our study considering the effect of differences in the treatment protocol for each clinical course on the MELD score.

In conclusion, the MELD score to be calculated in the early period in COVID-19 patients may be an easily applicable scoring system that can be used both in determining the clinical course of the disease and in predicting mortality. If 13 is taken as the cut-off value for the MELD score in COVID-19 patients, it would be appropriate to closely follow COVID-19 patients with a score above this score in terms of mortality development.

Ethical Consent: Ethics committee approval was obtained from the local ethics committee with the decision dated 06.06.2022, reference number 2022/07-85.

Conflict of Interest: The authors have no conflict of interest regarding this study.

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