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Fibrosis-4 Index as a Predictor for Disease Severity and Mortality in Patients with COVID-19

COVID-19 Hastalarında Hastalık Şiddeti ve Mortalite için Bir Öngörücü Olarak Fibrozis-4 Indeksi

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ABSTRACT

Objective: The Fibrosis-4 (FIB-4) index is a noninvasive marker of liver fibrosis in various patient populations. We examined whether there is a relationship between the severity and prognosis of COVID-19 disease and the FIB-4 index.

Materials and Methods: This study is cross-sectional and retrospective. The patients were divided into two groups: those hospitalized in the intensive care unit (ICU) and those hospitalized in the clinic (non- ICU).

Results: Of the 158 cases,86(54%) were male. Age, total bilirubin, AST levels and FIB-4 index were higher in ICU patients compared to non-ICUs ($p<0.001$,$p=0.002$, $p=0.003$, $p<0.001$ respectively). FIB-4 index non-survivors were also higher ($p=0.002$). When the effect of the FIB-4 index on the severity of COVID-19 disease and mortality was evaluated by ROC analysis, both ICU and non-survivors were found to be significant (respectively, FIB-4 score; AUC=0.705,95%CI:0.624-785,$p<0.001$; AUC=0.654,95%CI:0.566-742,$p=0.002$). When the FIB-4 index cut-off value for disease severity was taken as 2.19, 70.0% sensitivity and 60% specificity were found in predicting disease severity. Moreover, when the FIB-4 index cut-off value for mortality was taken as 2.19, 71.2% sensitivity and 53% specificity were found in predicting mortality.

Conclusions: The FIB-4 index is an independent predictor of severity and mortality in COVID-19 patients requiring ICU.

Keywords: COVID-19, FIB-4 index, mortality

ÖZ

Amaç: Fibrosis 4 (FIB-4) index çeşitli hasta popülasyonlarında karaciğer fibrozisini gösteren non invaziv bir belirteçdir. Çalışmamızda COVİD-19 hastalığının ciddiyeti ve mortalite ile FIB-4 skoru arasında ilişki olup olmadığını incelemeyi planladık.

Materyal ve Metot: Bu çalışma kesitsel retrospektiftir. COVID-19 tanısı doğrulanmış olup hastanede yatan 158 hastayı içermektedir. Hastalar yoğun bakım ünitesinde (ICU) yatanlar ve kliniğe yatırılanlar (non-ICU) olarak iki gruba ayrıldı.

Bulgular: Toplam 158 olgunun 86 (50%)'sı erkek idi. Yaş, total bilirubin, AST ve FIB-4 index yoğun bakım ünitesinde yatanlarda yoğun bakımda yatmayanlarla karşılaştırıldığında sırasıyla ($p<0,001$, $p=0,002$, $p=0,003$, $p<0,001$) idi. FIB-4 index hayatta kalmayanlarda daha yüsekti ($p=0,002$). FIB-4 skorunun COVİD-19 ciddiyetini ve mortaliteyi öngörmedeki etkisi ROC analizi ile değerlendirildiğinde hem yoğun bakımda yatan hemde hayatta kalmayanlarda anlamlı bulundu (sırasıyla AUC=0,705, 95%CI: 0.624-785, $p<0,001$; AUC=0,654, 95%CI:0,566-742, $p=0,002$). Hastalık şiddeti için FIB-4 indeks için cut-off değeri 2,19 olarak alındığında hastalık şiddetini öngörmede %70,0 duyarlılık ve %60 özgüllük bulunmuştur. Ayrıca, mortalite için FIB-4 indeksi için cut-off değeri 2,19 olarak alındığında, mortaliteyi öngörmede %71,2 duyarlılık ve %53 özgüllük bulunmuştur.

Sonuç: FIB-4 indeksi yoğun bakım gerektiren COVİD-19 hastalarının cidiyetini ve mortaliteyi belirlemede bağımsız bir öngördürücüdür.

Anahtar Kelimeler: COVİD-19, FİB-4 indeks, mortalite

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INTRODUCTION

Coronavirus 2019 disease caused by SARS-CoV-2 has a broad spectrum of clinical features (asymptomatic disease, pneumonia, acute respiratory distress syndrome (ARDS), and death).[1] Approximately 5% of coronavirus 2019 patients require intensive care follow-up.[2] The need for intensive care and mortality occur in advanced age, comorbidity (chronic obstructive lung disease, diabetes mellitus, hypertension, cardiovascular disease), and immunesuppressive conditions.[3]

COVID-19 affects various organs. It has been shown that approximately 14-78% of affected individuals have increased liver function tests.[4] It is thought that this transaminase elevation is caused by hepatocellular damage.[5] Elevated AST/ALT ratio from liver function tests, hyperbilirubinemia, and hypoalbuminemia are associated with significant clinical adverse events.[6]

Liver fibrosis mainly develops in patients with fatty liver disease associated with metabolic dysfunction (MAFLD),[7] chronic hepatitis, cirrhosis, liver failure, and hepatic carcinoma.[8,9] A simple and noninvasive FIB-4 index has been developed to predict clinical courses and predict hepatic fibrosis in patients with chronic HCV, chronic hepatitis B, and HIV/HCV coinfection.[10,11] However, there is very little research evaluating the relationship of the FIB-4 index with the severity of COVID-19 and prognosis.[12-14]

In this study, we wanted to show whether there is a relationship between liver FIB-4 and the severity of COVID-19 and mortality.

MATERIALS AND METHODS

Ethics Committee Approval: This study was planned according to the Declaration of Helsinki. Ethical approval was obtained by applying to the ethics committee. (Date: 30.06.2021, decision no: 331).

Subjects: A total of 158 patients diagnosed with COVID-19 by the real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) and hospitalized in the tertiary hospital were included in the study. Cases with pregnancy, hematological disease, cirrhosis, and viral hepatitis were excluded. The patients were divided into two groups. The first group was hospitalized in the clinic (non-ICU), and the second group was in the intensive care unit (ICU). ICU patients were severe and critical (ARDS, mechanical ventilation, sepsis). The diagnosis of the disease severity was made according to the WHO severity definition.[15] In addition, patients were divided into two as survivors and non-survivors. Demographic/clinical, laboratory features, and FIB-4 scores were compared between groups.

Analysis: All data were analyzed retrospectively. Complete blood count (CBC) samples and other laboratory tests were carried out using routine methods. The FIB-4 index was calculated according to the formula: FIB-4 = age (year) × AST (U/L)/ [√ALT (U/L) × platelet count (109/L)].10

Statistical Analysis: The conformity of the variables to the normal distribution was investigated using Kolmogorov-Smirnov. The continuous variables were shown as mean and standard deviation (SD) or medians of the 25th–75th percentile. Categorical associations were evaluated by using the $\chi 2$ test. If parametric tests were fulfilled, independent groups were examined by t-test; if not, the Mann-Whitney U test was used. Receiver operating curve (ROC) analysis was used to calculate for the FİB-4 index the required cut-off values to differentiate ICU and non- survivor patients with maximum sensitivity and specificity. Statistical significance was indicated by $p \leq 0.05$. Statistical analyses were done using the SPSS version 20.0 statistics software (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the total 158 cases, 54% were male. The mean age was 71.0±10.9 years in ICU patients and 57.7±17.4 years in non-ICU patients, and the difference was significant (p<0.001). There was no difference between the two groups regarding gender (p=0.055). Descriptive statistics showing the demographic and clinical findings of the patients are shown in table 1. As a comorbid disease, HT and CVD were more common in ICU patients than in non-ICU patients, and there was a significant difference (respectively, p=0.002, p<0.001). Neutrophil count, WBC, procalcitonin, CRP, sedimentation, ferritin, LDH, d-dimer, INR, FBG (fasting blood glucose), creatinine, AST and lactate levels were significantly higher in ICU patients than non- ICU patients (respectively, p< 0.001, p=0.003, p<0.001, p<0.001, p=0.006, p< 0.001, p< 0.001, p<0.001, p=0.012, p<0.001, p<0.001, p=0.003, p=0.014). Although platelet count was higher in ICU patients compared to non- ICU, there was no significant difference. Total cholesterol, LDL levels, and lymphocyte count were lower in ICU patients (respectively p=0.006, p=0.032, P<0.001). When the FIB-4 index was compared, the results were higher in ICU patients than in non-ICU patients (median (IQR); 2 (1.1-3.0) vs. 3.1(2.0-4.7), p<0.001) (Table 1).

Table 1. Comparison of COVID-19 patients' demographics and clinic characteristics between patients with intensive care unit and non-intensive care unit.

Variables	Non-ICU patients (n=79)	ICU patients (n= 79)	p
Age, year	57.7±17.4	71.0±10.9	0.001
Gender, F/M (%)	42/37 (58.3/43.0)	30/49 (41.7/57.0)	0.055
Diabetes mellitus, n (%)	25 (31.6)	33(41.7	0.130
Hypertension, n (%)	30 (37.9)	48 (60.0)	0.002
COPD, n (%)	5 (6.3)	7 (8.8)	0.411
CVD, n (%)	5 (6.3)	25 (31.6	0.001
Chronic renal failure, n (%)	5 (6.3)	10 (12.6)	0.121
Malignancy, n (%)	1 (1.2)	4 (5.0)	0.132
White blood cell count, 10^3/ mm^3	6.4± 2.3	8.2 ± 3.4	0.003
Neutrophil count, $10^3/mm^3$	3.66 (3.0-5.5)	7.9 (4.6-10.7)	0.001
Lymphocyte count, $10^3/mm^3$	1.3 (0.9-1.9)	0.7 (0.4-1.0)	0.001
Platelet count, $10^3/mm^3$	196± (78)	206 ± (82)	0.941
C-reactive protein, (CRP), mg/L	32 (14-89)	110 (68-173)	0.001
Procalcitonin, ng/mL	0.06 (0.04-2.0)	0.28 (0.12-1.1)	0.001
Sedimentatin, mm/h	43 (27-70)	66 (44-74)	0.006
Alanine transferase, (ALT), U/L	27 (18-42)	27 (16-39)	0.675
Aspartate transferase, (AST), U/L	33 (24-42)	42 (30-61)	0.003
Total bilirubin, mg/dL	0.56±0.24	0.74±0.32	0.002
D-dimer, ng/mL	561 (300-1080)	1230 (642-1937)	0.001
Ferritin, ugFEU/L	262 (122-604)	748 (428-1777)	0.001
INR	1.1 (1.0-1.2)	1.2 (1.1-1.3)	0.012
Lactate dehydrogenase, (LDH),U/L	290 (220-351)	453 (386-594)	0.001
Total cholesterol, mg/dL	157 ±35	137±44	0.006
Low-density lipoprotein, (LDL), mg/dL	100±26	89±32	0.032
Lactate,,mmol/L	1.6 (1.3-2.0)	2 (1.6-2.5)	0.014
Glucose, mg/dL	121±46	186±95	0.001
Creatinine, mg/dL	0.7 (0.6-0.9)	1.0 (0.7-1.8)	0.001
FIB-4 index	2 (1.1-3.0)	3.1 (2.0-4.7)	0.001

Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease, INR: international normalized ratio; Fib-4: Fibrosis 4 index.

52 (32.9%) patients were non-survival. The mean age of survivors was significantly lower (p<0.001). WBC count, neutrophil count, total bilirubin, ferritin, LDH, D-dimer, CRP, procalcitonin, sedimentation, lactate, and FIB-4 index were significantly higher among non-survivors. Although AST was elevated in non-survivors, it was not significant. A comparison of laboratory and clinical features of non-survivor and survivor patients is shown in Table 2. When the results were compared in terms of FIB-4 score, it was higher in non-survivors than in survivors (median (IQR); 2.1 (1.1-3.0) vs. 3.1(2.0-4.7), p<0.002). There was a positive correlation between FIB-4 index and age, CRP, lactate, ferritin, and total bilirubin (p=0.001, p=0.017, p<0.002, p=0.002 and p=0.001, respectively). There was a positive correlation between FIB-4 index and age, CRP, lactate, ferritin, and total bilirubin (p=0.001, p=0.017, p<0.002, p=0.002 and p=0.001, respectively) (Table 2).

When the effect of the FIB-4 index on the severity of COVID-19 disease and mortality was evaluated by ROC analysis, both ICU and non-survivors were found to be significant (respectively, FIB-4 score; AUC=0.705, 95%CI:0.624-785, p<0.001; AUC=0.654, 95%CI:0.566-742, p=0.002). When the cut-off value for the FIB-4 score was taken as 2.19, it had 70.0% sensitivity and 60% specificity, vs. 71.2% sensitivity and 53% specificity in predicting disease severity and mortality, respectively (Figure 1).

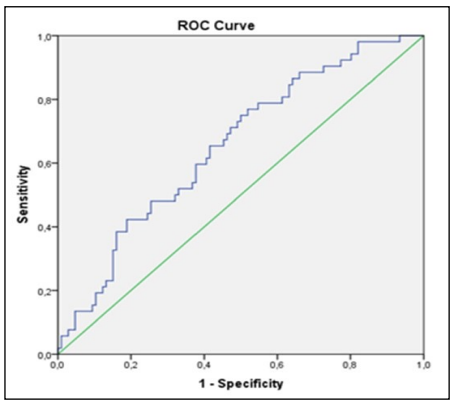

Figure 1. Receiver operating characteristic (ROC) curve for FIB-4 index in patients with survivor or non-survivor COVİD-19.

Table 2. Comparison of COVID-19 patients' demographics and clinic characteristics between survivors and non-survivors.

Variables	Survivor (n=79)	Non-survivors (n= 79)	p
Age, year	60.8± 17.1	71.7±9.9	0.001
Gender, F/M (%)	53 (50)/53(50)	19 (36)/33(64)	0.110
Systolic blood pressure, mm-Hg	123± 17	25±20	0.688
Diastolic blood pressure, mm-Hg	76±14	73±13	0.806
Diabetes mellitus, (%)	34 (32)	24 (46)	0.110
Hypertension, (%)	47 (44)	31 (59)	0.089
COPD, (%)	6 (5.6)	6 (11.5)	0.252
CVD, (%)	13 (12.2)	17 (32.6)	0.003
Chronic renal failure, (%)	7 (6.6)	8 (15.3)	0.105
Malignancy, (%)	1 (0.9)	4 (7.6)	0.031
Neutrophil count, $10^3/mm^3$	6.8±2.8	8.1 (3.2)	0.030
Lymphocyte count, $10^3/mm^3$	1.2 (0.8-1.6)	0.6 (0.4-1.0)	0.001
Platelet count, $10^3/mm^3$	199± (79)	205 ± (83)	0.674
C-reactive protein, (CRP), mg/L	52 (15-98)	113 (69-176)	0.001
Procalcitonin, ng/mL	0.08 (0.05-2.0)	0.32 (0.14-1.3)	0.001
Sedimentatin, mm/h	50 (30-70)	69 (39-78)	0.010
Alanine transferase, (ALT), U/L	27 (19-43)	27 (16-37)	0.510
Aspartate transferase, (AST), U/L	35 (25-46)	40 (25-57)	0.121
Total bilirubin, mg/dL	0.61±0.28	0.74±0.29	0.047
D-dimer, ng/mL	633 (330-1420)	1200 (589-2102)	0.009
Ferritin, ugFEU/L	351 (187-726)	758 (370-1487)	0.001
INR	1.1 (1.0-1.2)	1.2 (1.1-1.4)	0.008
Lactatedehydrogenase, (LDH),U/L	307 (242-397)	471 (385-650)	0.001
Total cholesterol, mg/dL	151 ±36	139±48	0.150
Low-density lipoprotein, (LDL), mg/dL	96±27	91±34	0.412
Lactate, mmol/L	1.6 (1.3-2.0)	2.1 (1.6-2.6)	0.004
Glucose, mg/dL	133±58	191±102	0.001
Creatinine, mg/dL	0.8 (0.6-1.0)	1.1 (0.7-1.9)	0.001
FIB-4 index	2.1 (1.3-3.4)	3.0 (2.1-4.6)	0.002

Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease, INR: international normalized ratio; Fib-4: Fibrosis 4 index.

DISCUSSION AND CONCLUSION

In this study, Neutrophil count, WBC, LDH, d-dimer, creatinine, AST, procalcitonin, CRP, ferritin levels, and advanced age of ICU patients were higher than the non-ICU patients. The effect of the FIB-4 score in predicting the severity and mortality of COVID-19 disease was statistically significant. The FIB-4 score was higher in ICU patients and non-survivors compared to non- ICU and survivors.

In previous studies, advanced age was shown to be associated with severe COVID-19.[16] Similarly, advanced age was present in ICU and non-survivor patients in our study. COVID-19 has a powerful and fatal course in individuals with comorbidity.[3] In studies, diabetes mellitus and coronary artery disease were shown to be the most common causes of comorbidity after hypertension, respectively.[17] In our research, similarly, hypertension, diabetes, and cardiovascular disease were common in ICU patients and non-survivors, respectively. In a previous study, the mortality rate in the ICU group was ≤49%, and in another study, 60%.[18,19] In this study, we found the mortality rate to be 34% in inpatients.

The most important process that plays a role in disease severity and prognosis in COVID-19 is the severe and uncontrolled inflammatory response caused by infection. Many factors that play a role in this inflammatory response are associated with severe illness and mortality. In a meta-analysis study, platelet count, AST, LDH, and ferritin were biomarkers for critical patients. On the other hand, in non-survivors, a relationship was found with platelet count, but no association was found between AST and LDH.[20] In other meta-analyses, significant decreases in lymphocyte count, platelets, and albumin were observed in patients with severe COVID-19 disease compared to non-serious. At the same time, elevated ALT, AST, total bilirubin, LDH, and d-dimer levels were found.[21,22] Similarly, in our study, procalcitonin, CRP, neutrophil count, WBC, creatinine, LDH d-dimer, ferritin, AST, and total bilirubin levels were significantly higher in ICU patients than in non-ICU patients. Although platelet count was higher in ICU patients than in non-ICU patients, there was no significant difference. Similarly, there was no difference in platelet count in non-survivor patients; although AST levels were high, there was no significant difference, and total bilirubin levels were significantly higher.

Liver damage is seen in severe COVID-19 patients.[1,22] The mechanisms behind COVID-19 liver injury are thought to be directly related to virus effects, the elevation of certain cytokine levels, hypoxemia, and shock.[23] Fibrosis may increase the risk of

developing an exacerbated inflammatory response in COVID-19 severe patients. Developing liver disease stimulates immune cells. Activated immune cells, cytokines, chemokines, and other inflammatory markers play a role in maintaining the chronic low-grade systemic inflammation state.[24] In an acute infection, IL-6 released from macrophages stimulates the synthesis of acute phase response proteins such as CRP, ferritin, complement, coagulation factors, etc., in hepatocytes.[25] We found correlations between CRP, ferritin, INR, and FIB-4 score. Similarly, another study found a correlation between CRP and FIB-4 score.[13] This suggests that the inflammatory response is exacerbated in patients with higher fibrosis markers. Studies have shown that elevated AST/ALT ratio, hyperbilirubinemia, and hypoalbuminemia among liver function tests are associated with significant adverse events in COVID -19 patients.[7] Ibanez-Samaniego et al. announced that the FIB-4 score is an independent predictor of disease prognosis in patients aged 35-65 years with COVID-19.[13] Li Y et al. showed that the FIB-4 score is associated with mortality in COVID-19 patients regardless of underlying conditions, including liver disease.[15] In another study, it was determined that the FIB-4 score was an independent predictor of mortality in COVID-19 cases, regardless of the severity of the disease.[13] In our study, AST and total bilirubin levels are high in ICU patients. In our study, the FIB-4 index was higher in ICU and non-survivors than in non-ICU and survivors ($p<0.001$; $p<0.002$). When the FIB-4 index cut-off value for disease severity and mortality was taken as 2.19, 70.0% sensitivity and 60% specificity were found in ICU patients in predicting disease severity; 71.2% sensitivity and 53% specificity in predicting mortality.

The FIB-4 score can be calculated quickly from blood sample data worldwide. Therefore, it can help predict the need for ICU and mortality in COVID-19 disease. At the same time, these bio-markers are vital for early diagnosing of patients at risk of critically ill and providing early intervention to improve prognosis.

In conclusion, the FIB-4 score is an essential and useful independent predictor of ICU need, disease severity, and mortality in COVID-19 patients. Although this study was conducted in a large cohort and a tertiary hospital, there were some limitations. These limitations are the single-center, retrospective design and the lack of anthropometric data due to the urgency of epidemics. FIB-4 index components are not liver-specific. FIB-4 index may be affected by disorders other than liver disease. Therefore, more prospective studies are needed.

Ethics Committee Approval: This study was planned according to the Declaration of Helsinki. The study was approved by Sakarya University Non -interventional Ethics Committee (Date: 30.06.2021, decision no: 331).

Conflict interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – AN; Supervision – AN, TG; Materials – AA, KI, ACG; Data Collection and/or Processing – SY, AA, KI, ACG; Analysis and/or Interpretation – AN, TK, SY; Writing – AN, TK.

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