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FIB-4 Index: Potential Predictor of Mortality in COVID-19 Patients

FIB-4 İndeksi: COVID-19 Hastalarında Potansiyel Ölüm Öngörücüsü

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Abstract

Objective: To evaluate the predictive value of the fibrosis-4 (FIB-4) index for mortality among patients with Coronavirus disease-2019 (COVID-19).

Methods: This retrospective study included 325 patients diagnosed with COVID-19 via reverse transcription-polymerase chain reaction at a tertiary care hospital from January 2021 to January 2022. We calculated the FIB-4 index using age, aspartate aminotransferase, alanine aminotransferase, and platelet count. Data on demographics, clinical characteristics, comorbid conditions, and outcomes were analyzed.

Results: Patients were categorized into survivors (56.6%, n=184) and non-survivors (43.4%, n=151). The median FIB-4 index was significantly higher in non-survivors [4.02 interquartile range (IQR) 2.48-8.62)] than in survivors [2.57 (IQR 1.69-3.95)], p<0.001. ROC analysis showed that the FIB-4 index had a moderate predictive accuracy for mortality (area under the curve =0.693). A FIB-4 index cut-off of >3.80 provided the best balance between sensitivity (53.90%) and specificity (74.46%).

Conclusion: The FIB-4 index serves as a reliable predictor of mortality in patients with COVID-19, surpassing traditional liver function tests in prognostic accuracy. It offers a practical tool for the early identification of patients at higher risk of adverse outcomes.

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

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) hastalarında fibrozis-4 (FIB-4) indeksinin mortalite açısından öngörücü değerini değerlendirmek.

Yöntem: Bu retrospektif çalışmaya Ocak 2021 ile Ocak 2022 arasında üçüncü basamak bir hastanede gerçek zamanlı-polimeraz zincir reaksiyonu ile COVID-19 tanısı konan 325 hasta dahil edildi. FIB-4 indeksi yaş, aspartat aminotransferaz, alanin aminotransferazve trombosit sayısı kullanarak hesaplandı. Demografik özellikler, klinik özellikler, komorbid durumlar ve sonuçlara ilişkin veriler analiz edildi.

Bulgular: Hastalar hayatta kalanlar (%56,6, n=184) ve hayatta kalmayanlar (%43,4, n=151) olarak kategorize edildi. Medyan FIB-4 indeksi hayatta kalanlarda [4,02 (çeyrekler arası aralık (ÇAA) 2,48-8,62)], hayatta kalanlara [2,57 (ÇAA 1,69-3,95)] kıyasla anlamlı derecede yüksekti, p<0,001. ROC analizi, FIB-4 indeksinin mortalite için orta düzeyde bir tahmin doğruluğuna sahip olduğunu gösterdi (eğri altında kalan alan =0,693). FIB-4 indeks kesme noktası >3,80, duyarlılık (%53,90) ve özgüllük (%74,46) arasındaki en iyi dengeyi sağladı.

Sonuç: FIB-4 indeksi, prognostik doğruluk açısından geleneksel karaciğer fonksiyon testlerini geride bırakarak, COVID-19 hastalarında mortalitenin güvenilir bir tahmincisi olarak hizmet vermektedir. Olumsuz sonuç riski daha yüksek olan hastaların erken tespiti için pratik bir araç sunar.

Anahtar Kelimeler: COVID-19, FIB-4 indeksi, mortalite

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Introduction

The Coronavirus disease-2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has posed unprecedented health challenges globally[1-3]. Since its emergence in late 2019, the virus has led to significant morbidity and mortality, requiring the medical community to identify reliable predictors that can guide patient management and improve outcomes[4,5]. Among the predictors investigated, the severity of infection and mortality rates have shown marked variability, influenced by a host of demographic, clinical, and biological factors[6-8].

Various scoring systems have been employed to predict outcomes in patients with COVID-19, underlining the necessity for accurate prognostic tools in managing the disease[9-11]. Among these, liver function, as reflected in parameters like fibrosis scores, has emerged as a critical element. The Fibrosis-4 (FIB-4) index, originally developed to assess liver fibrosis in patients with hepatitis C, has gained attention for its potential utility in other clinical settings[12]. This index, which incorporates age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, offers a practical tool to assess liver fibrosis. Recent studies have suggested that FIB-4 could also serve as a significant prognostic marker in patients with COVID-19, potentially correlating with disease severity and mortality[13].

The current study aimed to evaluate the predictive value of the FIB-4 index for mortality among COVID-19 patients.

Materials and Methods

This retrospective cohort study was conducted at a tertiary care hospital's emergency department from January 2021 to January 1, 2022. This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (number: 2023/514/255/4, date: 09.08.2023). The study encompassed all patients aged 18 years who presented to the emergency department and were diagnosed with COVID-19 based on a positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2. Eligible participants included all patients who tested positive for COVID-19 via reverse transcription-polymerase chain reaction during the study period. The exclusion criteria were patients under the age of 18, patients with liver disease, and those without complete medical records available for review.

Data were retrospectively collected from the hospital's electronic health records. The variables extracted included demographic information (age and gender), laboratory results, comorbid conditions, admission to intensive care units, and in-hospital mortality. These data elements were used to assess the severity of the disease and its outcomes in the study population.

The FIB-4 index was calculated for each patient using the following formula:

$$(age \times AST) / (platelets \times \sqrt{(ALT)})$$

Statistical Analysis

Statistical analyses were performed using SPSS software for Windows (Version 29, Chicago, IL, USA). Descriptive statistics will be used to summarize the demographic and clinical characteristics of the patients. The primary outcome of this analysis will be to assess the predictive power of the FIB-4 index for in-hospital mortality. To further evaluate the diagnostic performance of the FIB-4 index, receiver operating characteristic (ROC) curve analysis will be conducted. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the FIB-4 index at optimal cut-off values determined from the ROC analysis will also be reported. A p-value of 0.05 will be considered statistically significant.

Results

After applying the inclusion and exclusion criteria, the study was completed with 325 participants. The patients were divided into two groups: Survivors (56.6%, n=184) and non-survivors (43.4%, n=151). Various characteristics of the patients are summarized in Table 1. There was no statistically significant difference in median age between survivors [73.3 (interquartile range (IQR) 68-81)] and non-survivors [75 (IQR 68.4-81)] (p=0.379). No significant differences were observed in gender ratios between the groups (p=0.184).

While no significant difference was noted in median systolic blood pressure between the groups (p=0.598), a statistically significant higher median diastolic blood pressure was observed in the survivor group [72 (IQR 70-80) mmHg] compared with the non-survivor group [70 (IQR 65-80) mmHg] (p=0.019). The survivor group exhibited a significantly lower median pulse rate [83 (IQR 75-91) beats per minute] than the non-survivor group [95 (IQR 79-105) beats per minute (p<0.0019). Oxygen saturation was also significantly lower in the non-survivor group [92 (IQR 85-96) %] compared to the survivor group [95 (IQR 92-97) %] (p<0.001). No significant difference was found in the median body temperature between the groups (p=0.072).

Table 1. Comparison of various characteristics between the groups			
	Survivors (n=184)	**Non-survivors (n=141)**	**p-value**
Age (years)	73.3 (68-81)	75 (68.4-81)	0.379
Gender (man)	90 (50%)	81 (57.4%)	0.184
Systolic blood pressure (mmHg)	120 (110-135.25)	129 (110-144)	0.598
Diastolic blood pressure (mmHg)	72 (70-80)	70 (65-80)	0.019
Pulse (beats/min)	83 (75-91)	95 (79-105)	<0.001
SpO_2	95 (92-97)	92 (85-95)	<0.001
Body temperature (°C)	36.7 (36.2-37.2)	36.8 (36.4-37.5)	0.072
Chronic obstructive pulmonary disease	17 (9.2%)	17 (12.1%)	0.411
Diabetes mellitus	61 (33.2%)	38 (27%)	0.229
Hypertension	83 (45.1%)	53 (37.6%)	0.173
Congestive heart failure	12 (6.5%)	21 (14.9%)	0.013
Chronic renal failure	7 (3.8%)	19 (13.5%)	0.001
White blood cells (10^9/L)	6.3 (5-8.7)	8.4 (6.3-12.4)	<0.001
Neutrophil (10^3/uL)	4.5 (3.2-6.8)	6.8 (4.7-10.4)	<0.001
Lymphocite (10^3/mm^3)	1 (0.6-1.4)	0.8 (0.6-1.2)	0.034
Hemoglobin (g/dL)	12.5 (11.5-13.4)	11.8 (9.9-13.1)	0.005
Platelet (10^9/L)	195 (152-264)	217 (171-288)	0.023
Blood urea nitrogen (mg/dL)	44 (31-57)	64 (43-93)	<0.001
Albumin (g/dL)	34 (30-37)	32 (29-36)	<0.001
Aspartate aminotransferase (IU/L)	29 (22-41)	52 (36-97.5)	<0.001
Alanine aminotransferase (IU/L)	19 (12-33)	20 (13-33)	0.833
Creatinine (mg/dL)	0.87 (0.71-1.06)	1.11 (0.8-1.82)	0.004
Intensive care unit admission	19 (10.3%)	82 (58.2%)	<0.001
Fib-4 score	2.57 (1.69-3.95)	4.02 (2.48-8.62)	<0.001

When evaluating comorbid conditions, no significant differences were observed between the groups in the prevalence of chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and coronary artery disease (respectively; p=0.411, p=0.229, p=0.173, p=0.447). However, the incidence of chronic kidney disease and congestive heart failure was significantly higher in the non-survivor group (respectively; p=0.013, p=0.001).

The non-survivor group had significantly higher median values of white blood cell count, neutrophils, platelets, urea, AST, and creatinine compared with the survivor group (respectively; p<0.001, p<0.001, p=0.023, p<0.001, p<0.001, p=0.004). Conversely, median lymphocytes, hemoglobin, and albumin were significantly higher in the survivor group (respectively; p=0.034, p=0.005, p<0.001). No significant difference was observed in the median ALT levels between the groups (p=0.833).

The median FIB-4 score was significantly lower in the survivor group [2.57 (IQR 1.69-3.95)] than in the non-survivor group [4.02 (IQR 2.48-8.62)] (p<0.001) as shown in Figure 1.

The area under the receiver operating characteristic curve for the FIB-4 score predicting mortality was 0.693 [95% confidence interval (CI) 0.640-0.743] (p<0.001). At the optimal cut-off value for the FIB-4 score (>3.80) based on the Youden index, the sensitivity was 53.90 (95% CI 45.3-62.3), specificity was 74.46 (95% CI 67.5-80.6), PPV was 2.11 (95% CI 1.58-2.82), and NPV was 0.62 (95% CI 0.51-0.75) as depicted in Figure 2, Table 2).

Discussion

The FIB-4 index, as demonstrated in this study, offers significant predictive value for mortality among COVID-19 patients. This aligns with the growing body of literature suggesting the role of liver function metrics in

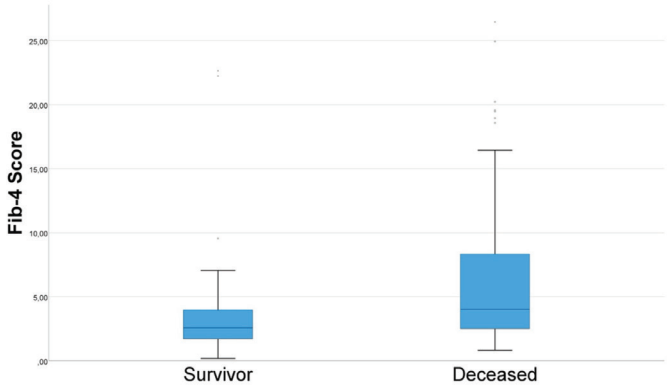

Figure 1. Comparison of Fib-4 scores between the groups

Fib-4: Fibrosis-4

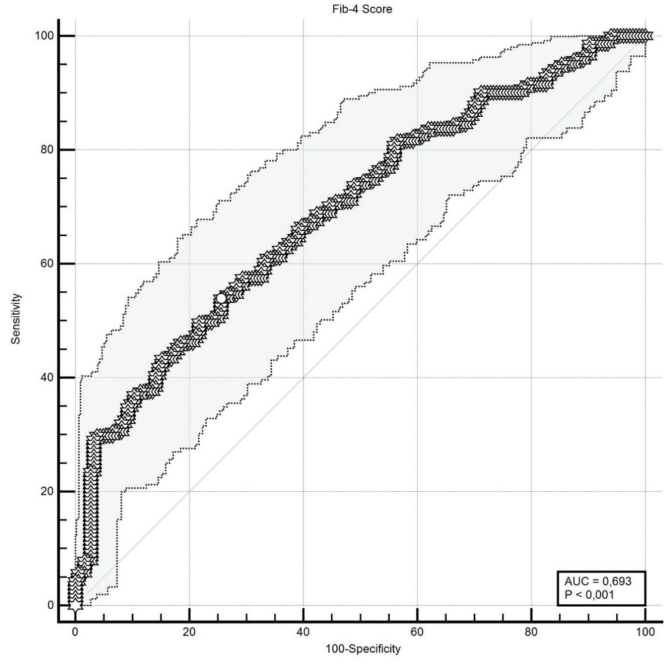

Figure 2. Area under the curve (AUC) analysis of the Fib-4 score in mortality prediction

Fib-4: Fibrosis-4

understanding the progression and outcomes of COVID-19. The pathophysiological linkage between liver dysfunction and COVID-19 may be attributed to the direct cytopathic effects of SARS-CoV-2 and systemic inflammation, leading to hepatocyte injury and altered liver enzyme levels.

Recent studies have reinforced this association. For instance, Pranata et al.[14] in their meta-analysis reported a strong correlation between higher FIB-4 scores and increased mortality rates in COVID-19 patients, with a calculated odds ratio significantly indicating worse outcomes. Similarly, Bucci et al.[15] found that a FIB-4 score greater than 3.25 was significantly associated with increased mortality, underscoring its utility over traditional liver transaminases and the AST-to-platelet ratio index for mortality prediction in emergency settings.

These findings are pivotal, considering the high prevalence of abnormal liver tests observed in COVID-19 patients, which has been widely reported as a marker of severe disease. For example, elevated levels of AST and ALT, which are components of the FIB-4 calculation, have been consistently linked with poor outcomes in these patients. The mechanism likely involves the systemic inflammatory response triggered by the virus, which not only impacts lung tissue but also affects the liver. This systemic inflammation, often referred to as a "cytokine storm," can intensify underlying liver conditions, thereby increasing the FIB-4 score[16-18].

However, the literature also presents some variability in the predictive accuracy of FIB-4 across different cohorts and settings. This variability can be partly attributed to differences in patient demographics, baseline liver health, and stage of COVID-19 at presentation. For instance, in settings with a high prevalence of underlying chronic liver diseases, the predictive value of FIB-4 may differ, as shown by studies that specifically looked at patients with conditions like non-alcoholic fatty liver disease[19].

Given the significant role of liver dysfunction in COVID-19 prognosis, FIB-4 serves not only as a tool for assessing liver fibrosis but also as a broader indicator of patient vulnerability

Table 2. Predictive performance of the Fib-4 score in terms of severity in COVID-19 patients

AUROC (95% CI)	Youden J	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
0.693 (0.640-0.743)	0.283	>3.809	53.9 (45.3-62.3)	74.46 (67.5-80.6)	2.11 (1.58-2.82)	0.62 (0.51-0.75)

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, AUROC: Area under the receiver operating characteristic, CI: Confidence interval, COVID-19: Coronavirus disease-2019, Fib-4: Fibrosis-4

to severe outcomes. This dual utility makes the FIB-4 index a valuable component of the clinical assessment tool in managing COVID-19, particularly in stratifying patients based on risk and optimizing resource allocation.

Study Limitations

This study, while comprehensive, is not without limitations. The retrospective nature and single-center design may limit the generalizability of the findings. In addition, the inherent biases associated with retrospective data collection and the potential for missing data could affect the accuracy of the FIB-4 scores and subsequent analyses. Future studies should validate these findings in a larger, multicenter cohort with a prospective design to mitigate these limitations.

Conclusion

The FIB-4 index is a robust predictor of mortality in COVID-19 patients, offering a simple, non-invasive measure of liver dysfunction and overall disease severity. This index could be particularly useful in emergency departments and other acute care settings to rapidly identify patients at a higher risk of severe outcomes, thereby guiding more targeted interventions and supportive care strategies.

Ethics

Ethics Committee Approval: This retrospective cohort study was conducted at a tertiary care hospital's emergency department from January 2021 to January 1, 2022. This study was approved by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (number: 2023/514/255/4, date: 09.08.2023).

Informed Consent: Written informed consent was not necessary because no patient data have been included in the manuscript.

Authorship Contributions

Surgical and Medical Practices: G.A.U., Concept: G.A.U., Design: G.A.U., Data Collection or Processing: İ.U., Analysis or Interpretation: İ.U., Literature Search: İ.U., Writing: G.A.U., İ.U.

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