The Relationship of Elevated Hepatic Fibrosis-4 Index Score with Pneumonia Severity Index and in Hospital Mortality Among COVID-19 Patients Admitted to Intensive Care Unit

Yoğun Bakıma Yatırılan COVID-19 Hastalarında Erken Dönemde Bakılan Yüksek Hepatik Fibrozis-4 Skoru ile Pnömoni Ciddiyet İndeksi ve Hastane İçi Mortalite Arasındaki İlişkinin Araştırılması

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ABSTRACT

Objective: We investigated the relationship hepatic fibrosis-4 (FIB-4) index score calculated in the early period and pneumonia severity index (PSI) and in-hospital mortality in patients hospitalized in the intensive care unit (ICU) due to new severe acute respiratory syndrome coronavirus-2 infection.

Methods: Seventy six consecutive patients diagnosed with coronavirus disease-2019 (COVID-19), hospitalized in the ICU due to hypoxemia, and selected consecutively were included. COVID-19 infection was diagnosed using real-time reverse transcription-polymerase chain reaction (RT-PCR) in nose and throat swab samples. The diagnosis of pneumonia was confirmed by showing typical ground-glass opacities and areas of subsegmental consolidation in lung computed tomography examinations of patients previously diagnosed with COVID-19 by RT-PCR. Hepatic FIB-4 index score and PSI score was calculated separately for each patient. In the statistical method, the independent samples t-test and Mann-Whitney U test were used to compare quantitative data. A chi-square test was used to compare qualitative data.

Results: The FIB-4 value and PSI value were significantly higher (p<0.05) in the mortality group than in the non-mortality group. Also, there was no significant statistical difference between the two groups in terms of the other laboratory parameters (p>0.05) FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive of 95.2%, specificity of 97.6%, and negative predictive value of 75.9%

Conclusion: High FIB-4 index and PSI score detected in the early period in patients admitted to the ICU due to COVID-19 seem to be predictors of in-hospital mortality.

Keywords: Coronavirus infection, liver fibrosis, pneumonia, prognostic factors

ÖZ

Amaç: Yoğun bakım ünitesine (YBÜ) yatırılan, yeni şiddetli akut solunum yolu sendromu koronavirüs-2 enfeksiyonu nedeniyle yatırılan hastalarda erken dönemde hesaplanan hepatik fibrozis-4 (FIB-4) indeks skorunun, pnömoni ciddiyet indeksi (PSI) ve hastane içi mortaliteyle ilişkisini araştırılmıştı.

Gereç ve Yöntem: Koronavirüs hastalığı-2019 (COVID-19) tanı konulan, hipoksemi nedeniyle YBÜ’ye yatırılan ve ardından seçilen 76 hasta dahil edildi. Burun ve boğaz sütunluk örneklerinde gerçek zamanlı ters transkripsiyon-polimeraz zincir reaksiyonu (RT-PCR) kullanılarak COVID-19

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The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues to threaten public health by being an important cause of mortality due to newly developing mutations and novel variants despite widespread use of vaccination worldwide (1-3). Among patients admitted to intensive care unit for pneumonia and hypoxemia, determining patients at high risk of death early in the infection and treating them more aggressively are particularly important. For this purpose, several risk scores have been developed to predict mortality, which are used in daily practice (4,5). However, some of those scores are too complex, difficult to calculate in daily practice, and time-consuming for clinicians. In this context, there is a need for developing novel risk scores that are relatively simple, inexpensive, and easy-to-calculate that use blood tests routinely studied in daily practice.

Elevation of liver enzymes is common in SARS-CoV-2 infection and has been related to a worse prognosis (6,7). In this regard, some hepatic risk scores predict long-term and short-term prognosis in SARS-CoV-2 infection (8,9). Hepatic fibrosis-4 (FIB-4) index score is one of those hepatic fibrosis scores that can be easily calculated with 4 simple parameters including age, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and platelet (PLT) count (9). Although some of the previous studies have provided important data suggesting that a high FIB-4 score predicts mortality in coronavirus disease-2019 (COVID-19) patients, their overall number is small; moreover, there is a limited number of studies on COVID-19 patients admitted to intensive care unit, necessitating new studies and data on this subject.

In our study, we investigated the relationship of hepatic FIB-4 index score with pneumonia severity index (PSI) and in-hospital mortality among patients admitted to intensive care unit with SARS-CoV-2 infection.
This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021). Before study entry, written informed consent was obtained from the patients themselves when they could provide it, or their relatives when they were not.

**Statistical Analysis**

Study data were analyzed using SPSS 27.0 statistical software for Windows (SPSS Inc., Chicago, IL, ABD). Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage. The normality of the distribution of continuous variables was tested using Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used to compare quantitative data. Chi-square test was used to compare qualitative data. Receiver operating characteristics curve was used to calculate the cut-off values to discriminate deceased patients with maximum sensitivity and specificity. A p value of less than 0.05 was considered statistically significant.

**RESULTS**

Demographic data, comorbidities and symptoms of patients are shown in Table 1. The age and gender distribution of the patients did not differ significantly between the groups with and without mortality (p>0.05). Cancer, congestive heart failure, stroke, chronic kidney disease, chronic liver disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, coronary artery disease and extracorporeal membrane oxygenation rates did not differ significantly between groups with and without mortality (p>0.05).

Laboratory results of patients are summarized in Table 2. Arterial PH in the mortality group was significantly (p<0.05) lower than the non-mortality group. The rate of mechanic ventilator use in the mortality group was significantly (p<0.05) higher than the non-mortality group. PaO₂ and SPO₂ values were significantly lower (p<0.05) in the mortality group than in the non-mortality group.

The FIB-4 value and PSI value were significantly higher (p<0.05) in the mortality group than in the non-mortality group (Table 2, Figure 1). Also, there was no significantly statistical difference between two groups in terms of the other laboratory parameters (p>0.05) (Table 2).

Additionally, ICU length of stay did not differ significantly (p>0.05) between groups with and without mortality.

FIB-4 value was significantly predictive [under the curve 0.835 (0.742-0.929)] in differentiating patients with and without mortality. For a cut-off value of 5.4, FIB-4 had a sensitivity of 60.6%, positive predictive 95.2%, specificity of 97.6%, and negative predictive value of 75.9% (Figure 2).

**DISCUSSION**

Our study has two important results. Firstly, a high hepatic FIB-4 score calculated at the time of diagnosis appears to be correlated with in-hospital mortality. Secondly, a high PSI score calculated at the time of diagnosis was higher in a patient with mortality. The reason why mortality was higher in patients with higher FIB-4 score was probably that PSI score was also higher in the same patients.

SARS-CoV-2 infection is a disease characterized by a multi-organ involvement, and mild-to-moderate liver enzyme elevation is frequently encountered during its course (13). Elevated ALT, AST levels combined with mildly elevated bilirubin levels are usually observed (9). The plausible mechanisms for elevating liver enzymes include the direct cytopathic effect of the virus on hepatocytes and cholangiocytes, exaggerated immune response during infection, side effects of some antiviral drugs used to treat the infection, and the occurrence of septicemia during the infection (9,14). However, several studies have also shown that elevated liver enzymes have prognostic significance in SARS-CoV-2 infection (15,16). In this context, it is thought that some hepatic risk scores could be used to determine prognosis. Hepatic FIB-4 index is a useful risk score that can be readily calculated using several laboratory parameters that are widely used to diagnose and monitor COVID-19 patients in daily practice; additionally, many studies have shown that FIB-4 index has prognostic significance in patients with COVID-19 (8,17,18). There are several probable causes of an elevated FIB-4 index in COVID-19 infection. Among these, direct hepatocellular injury caused by the virus, systemic inflammation and cytokine storm, increased pulmonary artery pressure and right chamber pressures are the main ones (17). In a study that included 202 patients admitted to hospital due to COVID-19 infection, a high FIB-4 index was correlated with mortality; there were also positive correlations between a high FIB-4 index and viral load, and monocyte-related cytokines such as interleukin-6 (17). In a more comprehensive, retrospective, multi-center cohort study, Park et al. (18) showed that a high FIB-4 index score was a strong predictor of mortality. Similarly, Xiang et al. (19) demonstrated that FIB-4 index calculated at an early period was an important prognostic marker in patients hospitalized for COVID-19 infection. The authors found that patients with FIB-4 >3.25 had more than 12 times greater need for high-flow oxygen and 11 times greater rate of progression to severe disease, particularly at an early
disease period (19). Our results also support those previous observations. Intensive care unit patients who had a higher FIB-4 index early in the disease course suffered a worse prognosis a higher mortality rate.

Another important finding of our study is higher PSI score in patient with mortality. In fact, previous studies have shown that PSI index predicts mortality at the early period of COVID-19 (12,20). For example, Satici et al. (12) found that PSI more effectively predicted 30-day mortality in hospitalized patients than CURB-65, another risk score with proven effectiveness for predicting mortality in community-acquired pneumonia. Similarly, another retrospective study including 1,181 patients showed that PSI was superior than CURB-65 for predicting 30-day mortality (21). However, CURB-65 score was better in predicting patients who needed critical care (21). Hence, patients with a higher PSI score are older and have a higher number of comorbidities, worse vital signs, and a greater rate of multi-organ dysfunction. This makes the finding

|             | AUC  | 95% Confidence interval | p   |
|-------------|------|------------------------|-----|
| FIB-4       | 0.835| 0.742 - 0.929          | 0.000 |

Figure 1. Comparison of FIB-4 index and PSI results between living and deceased patients
FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index

Figure 2. The result of receiver operating characteristic curve
ROC: Receiver operating characteristic, FIB-4: Fibrosis-4 index, PSI: Pneumonia severity index, AUC: Area under the curve
of a higher mortality rate among COVID-19 patients with a higher PSI score more understandable. Additionally, one must expect that FIB-4 index, which is calculated using age, PLT count, and basic liver function tests ALT and AST, will be particularly higher in older patients who more commonly have multi-organ failure and liver injury, and a higher PSI score. In conclusion, high FIB-4 index and PSI score calculated early during SARS-CoV-2 infection indicates that these two parameters may independently predict mortality at an early stage. Furthermore, the combined use of these two scores, particularly when both of them are elevated, can allow physicians to diagnose SARS-CoV-2 infection requiring critical care at an early period, and to lower mortality by more aggressively treating such patients.

**Study Limitations**

Our study has some limitations. A relatively small number of patients is an important limitation. Other important limitations include the lack of having a basal abdominal ultrasonography and not excluding underlying liver diseases that could have increased FIB-4 index. Moreover, the lack of using other hepatic FIB scores such as AST-to-PLT ratio index, aminotransferase

| Table 1. Comparison of demographic data, comorbidities and symptoms of patients |
|--------------------------------|---------------------------------|-------------------------|
|                                | Mortality (-)                   | Mortality (+)          |
|                                | Mean ± SD/n-%                   | Median                 | Mean ± SD/n-% | Median | P       |
| Age                            | 62.8±16.2                       | 63.0                   | 65.1±13.2     | 65.0   | 0.525*  |
| Gender                         |                                 |                        |               |        |        |
| Female                         | 13/31.0%                        | -                     | 12/36.4%     | -      | 0.622** |
| Male                           | 29/69.0%                        | -                     | 21/63.6%     | -      |        |
| Cancer                         | 5/11.9%                         | -                     | 7/21.2%      | -      | 0.275** |
| Congestive heart failure       | 7/16.7%                         | -                     | 7/21.2%      | -      | 0.616*  |
| Stroke                         | 4/9.5%                          | -                     | 0/0.0%       | -      | 0.126** |
| Chronic kidney disease         | 7/16.7%                         | -                     | 9/27.3%      | -      | 0.266*  |
| Chronic liver disease          | 2/4.8%                          | -                     | 0/0.0%       | -      | 0.501*  |
| Hypertension                   | 21/50.0%                        | -                     | 15/45.5%     | -      | 0.696*  |
| DM                             | 14/33.3%                        | -                     | 11/33.3%     | -      | 1.000** |
| COPD                           | 2/4.8%                          | -                     | 1/3.0%       | -      | 1.000** |
| Asthma                         | 3/7.1%                          | -                     | 4/12.1%      | -      | 0.462** |
| Coronary artery disease        | 1/2.4%                          | -                     | 1/3.0%       | -      | 1.000** |
| ECMO                           | 0/0.0%                          | -                     | 2/6.1%       | -      | 0.190** |

**Symptoms**

|                                    | Mortality (-) | Mortality (+) | P     |
|------------------------------------|---------------|---------------|-------|
| High fever                         | 19/45.2%      | 14/42.4%      | 0.807*|
| Cough                              | 13/31.0%      | 11/33.3%      | 0.826*|
| Dyspnea                            | 31/73.8%      | 24/72.7%      | 0.916*|
| Myalgia                            | 4/9.5%        | 5/15.2%       | 0.457*|
| Headache                           | 1/2.4%        | 4/12.1%       | 0.093*|
| GIS symptoms                       | 3/7.1%        | 1/3.0%        | 0.626*|
| Loss of taste and smell            | 0/0.0%        | 0/0.0%        | 1.000*|
| Pleural effusion                   | 9/21.4%       | 9/27.3%       | 0.556*|
| Lung involvement                   | 34/81.0%      | 25/75.8%      | 0.586*|

SD: Standard deviation, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, ECMO: Extracorporeal membrane oxygenation, GIS: Gastrointestinal system, *Mann-Whitney U test, **chi-square test
ratio to alanine in addition to FIB-4 index may also be considered a limitation. Another important limitation is that other risk scores predicting mortality in COVID-19 infection, such as Severe Community-Acquired Pneumonia, COVID-GRAM score, and CURB-65 score, were not calculated and thus their correlation to FIB-4 was not analyzed (22, 23).

### CONCLUSION

FIB-4 index, and PSI score calculated at an early period among patients admitted to intensive care unit for COVID-19 appears to be good predictors of in-hospital mortality. More extensive, randomized studies are needed on this subject.
ETHICS

Ethics Committee Approval: This study complied with the criteria of Helsinki Declaration and approved by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee (decision no: 91, date: 21.01.2021).

Informed Consent: Informed consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: C.E., H.G., A.Y., Concept: E.D., O.O., Design: E.D., Data Collection or Processing: A.Y., R.C., H.G., Analysis or Interpretation: E.D., O.O., H.G., Literature Search: E.D., R.C., A.Y., Writing: E.D.

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