

The FIB-4 Index Is Associated with Need for Mechanical Ventilation and 30-day Mortality in Patients Admitted with COVID-19

^{1,2,3} Richard K. Sterling, MD, MSc, ³ Tavis Oakes, ⁴ Tamas S. Gal, PhD. ² Michael P. Stevens, MD, MPH, ⁵ Marjolein deWit, MD, and ^{1,3} Arun J. Sanyal, MD

¹ Division of Gastroenterology, Hepatology, and Nutrition, ² Division of Infectious Diseases, ³ C. Kenneth and Dianne **Wright Center** for Clinical and Translational Research, ⁴ Department of Biostatistics, and ⁵ Division of Pulmonary Medicine and Critical Care.

Virginia Commonwealth University, Richmond, Virginia

Corresponding author:

Richard K. Sterling, MD, MSc
1200 E Broad Street, West Hospital, Room 1478
VCU Medical Center
Richmond, VA 23298-0341
Ph: 804-828-9034
Fax: 804-828-5348
Richard.sterling@vcuhealth.org

Summary: The FIB-4 index, a simple tool developed to predict hepatic fibrosis, was found to independently be associated with need for mechanical ventilation and 30-day mortality in hospitalized patients with COVID-19.

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Abstract: The fibrosis-4 index (FIB-4), developed to predict fibrosis in liver disease, was used to identify patients with COVID-19 who will require ventilator support as well as associated with 30-day mortality. Multivariate analysis found obesity (OR 4.5), diabetes (OR 2.55), and FIB-4 \geq 2.67 (OR 3.09) independently associated with need for mechanical ventilation. When controlling for ventilator use, gender, and comorbid conditions, FIB-4 \geq 2.67 was also associated with increased 30-day mortality (OR 8.4; 95% CI 2.23-31.7). While it may not be measuring hepatic fibrosis, its components suggest that increases in FIB-4 may be reflecting systemic inflammation associated with poor outcomes.

Key Words: COVID-19, FIB-4, Respiratory Failure

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Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), can be associated with a severe systemic disease leading to respiratory failure and the need for mechanical ventilation [1]. Patients with underlying medical comorbidities, such as respiratory, cardiac, and liver disease, diabetes mellitus (DM), and obesity are at higher risk for respiratory failure [1-5]. Therefore, prediction factors are needed to help front line providers to identify who might be at higher risk for intensive care and ventilator support for respiratory failure.

COVID-19 has been associated with liver injury [6]. The fibrosis-4 index (FIB-4), developed to predict advanced fibrosis in those with liver disease has four components: age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count (PLT) [7]. Recent studies show these parameters may be affected by other systemic diseases, such as COVID-19 through non-hepatic mechanisms, including systemic inflammation and/or bone marrow suppression [8]. Our aims were to determine if FIB-4, a simple tool available to front line providers, would be associated with the need for mechanical ventilator support, and 30-day mortality among hospitalized patients with COVID-19.

Patients and Methods

Electronic medical records (EMR) were used to identify all patients admitted to Virginia Commonwealth University Medical Center in Richmond, Virginia, from February-May 2020 with confirmed COVID-19 by polymerase chain reaction (PCR). Because de-identified EMR data were used, institutional review board (IRB) was not required. Demographic data (age, gender, race), body mass index (BMI), obesity

(BMI \geq 30 kg/m²), existing respiratory, cardiac, liver, and diabetes mellitus (DM) disease by ICD-10 codes, from the index hospitalization, any previous hospital or ambulatory visit, and any previous billing diagnosis, AST, ALT, and PLT count were collected on the day of admission. FIB-4 was calculated ($\text{age} \times \text{AST} / \text{PLT} \times \text{ALT}^{1/2}$) and categorized as $<$ or \geq 2.67 or $<$ or \geq 3.25 [7, 9].

Data were presented by mean and standard deviation (SD) or median and interquartile range (IQR) or frequency and percent. The primary outcome was need for mechanical ventilator support during admission. Secondary endpoints were factors associated with increased FIB-4 and 30-day mortality. Factors associated with ventilator use, increased FIB-4, and 30-day mortality were assessed using Student's t test or Wilcoxon/Kruskal-Wallis test. Categorical variables were compared by chi-square. Factors identified in univariate analysis ($p < .02$) were assessed by multivariate analyses. Because of potential co-linearity between known liver disease and increased FIB-4, the model was run both with and without known liver disease. Survival was considered if the patients were discharged alive or remained hospitalized until day 30. Cox proportional hazard models were used to assess for factors on admission associated with 30-day survival. All data analyses were done using JMP 15 (SAS, Cary, NC).

Results

Between February and May, 2020, 256 patients were admitted: mean age was 58.7 years, 27% White and 57% African American (AA), 55% male, mean BMI of 32 kg/m², and 48% obese. The median duration of stay was 7 days (IQR 3-12). Coexisting respiratory, cardiac, liver diseases, and DM were observed in 24%, 28%, 6%, and 47%, respectively. The mean FIB-4 was 2.27 and 52% and 42% had FIB-4

≥ 2.67 and 3.25 , respectively. Those with increased FIB-4 were more likely White (33% vs. 18%; $p < .0001$), to have DM (54% vs. 44%; $p = .09$), and less likely to be obese (42% vs. 56%; $p = .05$). We did not observe an association with known liver disease and FIB-4 at the 2.67 ($p = .14$) or 3.25 ($p = .08$) thresholds. Admission to the intensive care unit (ICU) and need for ventilator support was observed in 18%.

Table 1 shows factors associated with need for ventilator support. Univariate analysis identified higher BMI (36 vs. 31 kg/m^2 ; $p = .01$), obesity (75 vs. 40%; $p < .0001$), history of respiratory disease (49 vs. 24%; $p = .001$), DM (73 vs. 42%; $p = .0001$), AST (69 vs. 61 U/L; $p = .01$), FIB-4 (4.1 vs 3.6; $p = .029$), FIB-4 ≥ 2.67 (70 vs. 48%; $p = .007$), FIB-4 ≥ 3.25 (61 vs. 38%; $p = .004$) and higher 30-day mortality (35 vs 6%; $p < .0001$). Multivariate analysis found obesity (OR 4.5; 95% CI 1.98-10.27), DM (OR 2.55; 95% CI 1.13-5.75), and FIB-4 ≥ 2.67 (OR 3.09; 95% CI 1.38-6.93) to be independently associated with need for ventilation. Similar results were seen when liver disease was included into the model. When controlling for comorbidities (BMI, DM, respiratory, cardiac, and liver diseases) and FIB-4, the c-statistic of the model associated with ventilator support was 0.79 (**Figure 1**). The sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of a FIB-4 ≥ 2.67 associated with ventilator use was 70%, 51%, 24% and 88%, respectively. When analyses using the higher FIB-4 threshold of 3.25 was used, the results were similar but with lower sensitivity (61%) and higher specificity (62%) PPV (27%) and NPV (90%). When the individual components of FIB-4 (age, AST, ALT, and platelet count) were substituted for FIB-4, none were independently associated with ventilator use.

Of the 256 patients hospitalized for COVID-19, 12% died within 30 days (mean 9 ± 5) days. Thirty-day mortality was associated with male gender (73 vs. 53%; $p = .036$),

respiratory (56 vs. 24%; $p=.0003$) and cardiac (50 vs. 25%; $p=.004$) diseases, DM (66 vs. 45%; $p=.02$), ICU (36% vs. 16%; $p=.007$), ventilator use (53 vs. 13%; $p<.0001$), and FIB-4 ≥ 2.67 (88 vs. 47%) or ≥ 3.25 (82 vs. 36%)(both $p<.0001$). When controlling for ventilator use, gender, and comorbid conditions, FIB-4 ≥ 2.67 was associated with increased 30-day mortality (OR 8.4; 95% CI 2.23-31.7). The hazard ratio (HR) for FIB-4 ≥ 2.67 was associated with 30-day mortality was 1.68; 95% CI 1.19-2.38: $p=.003$).

Discussion

A major challenge facing emergency room and front-line providers is predicting which patients with COVID-19 will develop respiratory failure and the need for ventilator support. Our data show that an increased FIB-4, a simple index, composed of age, AST, ALT, and platelet count, when combined with BMI and history of diabetes and respiratory disease, may help identify which patients may need ICU care and ventilator support. While the known history of liver disease in our cohort was low (6%), an increased FIB-4 was independently associated with a need for ICU care and ventilator support.

COVID-19, like any severe systemic illness, can be associated with systemic inflammation and increases in liver enzymes can be seen [6, 8, 10]. Therefore, it was not surprising that FIB-4 was increased in our cohort of hospitalized patients with PCR confirmed COVID-19. Increased severity of COVID-19 was reported in a cohort of patients with nonalcoholic fatty liver disease (NAFLD) with increased FIB-4 [4]. However, it was unclear if this represents the severity of underlying liver disease or a direct effect of SARS-CoV-2. In a recent study from the Department of Veterans Affairs (VA) of 585 who tested positive, 297 were hospitalized [11]. Among these,

122 (21%) required ICU care. When adjusted for significant clinical factors (DM, kidney, cardiovascular, and respiratory diseases), FIB-4 > 3.25 had an adjusted OR of 8.73 (95% CI 4.11-18.56) for hospitalization and OR 8.40 (95% CI 2.90-24.28) for ICU admission compared to those with FIB-4 < 1.45. Similar to that study, we did not observe an impact of AA race on COVID-19 disease severity. In another study of 160 hospitalized patients with COVID-19 from Spain, cardiovascular risk factors (OR 5.05; 95% CI 1.90-13.39), respiratory disease (OR 4.54; 95% CI 1.36-15.10), C-reactive protein (OR 1.012; 95% CI 1.006-1.017) and increased FIB-4 \geq 2.67 (OR 3.41; 95% CI 1.30-8.92) was observed in those admitted to the ICU [12]. They also observed that increased FIB-4 \geq 2.67 was more frequent in those who required ventilator support (37.8% vs. 18.3%; $p=0.0009$). Our data also support DM [2] and obesity as risk factors for COVID-19 disease severity [4, 12].

Of the components of FIB-4, only AST was significantly higher in those who required ventilator support. However, when the components of FIB-4 were substituted in the model, including AST, none were significantly associated with respiratory failure suggesting that it is the combination in the FIB-4 index and not its components that helps predict COVID-19 severity. The relationship of increased AST to ICU admission or ventilator support was seen in other studies [2, 12, 13]. However, unlike at the case of the Veterans' cohort [11], we did not observed differences in age, ALT, or platelet count. Regardless of these differences, our data confirm the independent association between increased FIB-4 and COVID-19 severity as measured by respiratory failure and need for ventilator support. Unlike the study by Ibanez-Samamiego that used a FIB-4 cutoff of 2.67 for those with NAFLD [9], we use both the NAFLD threshold as well as the higher cutoff of 3.25 used for viral hepatitis [7] also used by Rentsch [11]. Although our cohort had a high frequency of

increased FIB-4 (52% had FIB-4 > 2.67 and 42% had FIB-4 > 3.25), our cohort had low prevalence of known underlying liver disease (6%) which was not higher in those needing ICU or ventilator support. The choice threshold of any biomarker must balance sensitivity and specificity. Because a threshold of 2.67 had higher sensitivity (70%), with similar PPV and NPV compared to 3.25, we recommend it as a tool for future studies where the prevalence of viral hepatitis and known liver disease is low. However, the strength of FIB-4 may be in its high NPV to identify those who will not need mechanical ventilation. While FIB-4 is not assessing liver fibrosis, it may be a global score for systemic inflammation that has been associated with COVID-19 that is producing increased AST [6, 8, 10, 12]. In support of FIB-4 associated with non-liver related outcomes, a recent study found that increased FIB-4 was associated with outcomes after intracranial hemorrhage while the NAFLD fibrosis score did not [13], suggesting that FIB-4 has unique properties to assess outcomes not related to fibrosis or NAFLD. Finally, while some studies have observed higher mortality in AA with COVID-19 [14] we did not observe any difference in race or gender between those who required ventilator use and those that did not.

Our study has several important limitations. Our data and outcomes were determined by de-identified data obtained from our EMR, therefore if past medical conditions were not recorded, our data may have been affected. In addition, we did not have historical laboratory data to determine if increased liver enzymes were new and related to COVID-19 or chronic and due to existing liver disease which may impact COVID-19 severity [4]. Furthermore, we could have underestimated chronic liver disease and clinically silent cirrhosis that was not captured by the ICD-10 codes used. Importantly, we also were not able to capture data on need for high flow oxygen upon presentation to the health system. We also were not able to capture

days to respiratory failure. Although our cohort is of moderate size and reflective of patients in our geographic area, it does include patients of AA and White races and both genders. Although we did not observe a difference in age between those who did or did not require ventilator support, because age can influence FIB-4 (it is in the numerator), the inclusion of those with age >70 (25% of our cohort), may have overestimated the significance of FIB-4 in predicting respiratory failure and its wide 95% confidence interval. Lastly, we were not able to capture in the EMR if patients had been in clinical trials with experimental treatments for COVID-19 which may have impacted the utility of FIB-4 to predict 30-day mortality. Future studies in larger longitudinal cohorts that include adjustment for COVID-19 treatments, need for high flow oxygen upon presentation, and additional comorbidities, such as the Charleston Comorbidity Index [15], are needed to confirm the utility of FIB-4 and to identify an optimal cutoff as an independent index to predict COVID-19 disease severity.

In conclusion, FIB-4, a simple index, can be used by front line providers to identify patients with COVID-19 who may require ICU admission for ventilator support and have higher 30-day mortality. While it may not be measuring hepatic fibrosis, its components suggest that increases in FIB-4 may be reflecting systemic inflammation associated with poor outcomes.

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Table 1. Demographics of Cohort and Factors Associated with Ventilator Status

	Ventilation Yes	Ventilation No	Univariate p value	Multivariate OR; 95% CI: p value
N	45	211		
Age [^]	61.3 (12.8)	57.9 (18.6)	0.20	
Race (% White/Black/Other)	28/62/10	26/56/18	0.5	
Gender (% male/female)	53/47	56/44	0.75	
BMI (kg/m ²) [^]	35.6 (9)	30.9 (11)	0.01	
BMI ≥ 30 kg/m ² (% Obese)	75	40	<0.0001	4.5; 95% CI 1.98-10.27; p=0.0003
History of Respiratory Disease (%)	48.9	24.2	0.0013	.09
History of Cardiac Disease (%)	31	27	0.58	
History of Liver Disease (%)	6.7	5.7	0.8	.7
History of Diabetes Mellitus (%)	73	42	0.0001	2.55; 95% CI 1.13-5.75; p=.023
AST (U/L) ^{^^}	60 (40-77)	46 (32-67)	0.01	
ALT (U/L) ^{^^}	30 (20-43)	26 (16-45)	0.31	
Platelet Count (x 1000) [^]	223 (109)	220 (96)	0.7	
FIB-4 [^]	4.15 (2.5)	3.6 (3.28)	0.029	
FIB-4 ≥ 2.67 (%)	70	48	.007	3.09; 1.38-6.93: p=.006
FIB-4 ≥ 3.25 (%)	61	38	.004	2.9; 1.35-6.39: p=.006
ICU (%)	62	9	<0.0001	
Ventilator (%)	100	0	<.0001	
Length of Stay (days) [^]	16.9 (9.6)	7.1 (7)	<0.0001	
30-day mortality (%)	35	6	<0.0001	

[^] mean +/- SD ^{^^} median (IQR)

Figure 1. Area under the ROC curve (AUC) of the model including FIB-4 \geq 2.67, known respiratory disease, cardiac disease, liver disease, diabetes mellitus, and obesity. AUC 0.79.

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Figure 1. Area under the ROC curve (AUC) of the model including FIB-4 > 2.67, known respiratory disease, cardiac disease, liver disease, diabetes mellitus, and obesity.

