Fibrosis-4 Predicts the Need for Mechanical Ventilation in a National Multiethnic Cohort of Corona Virus Disease 2019

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Simple tests of routine data are needed for those with severe acute respiratory syndrome coronavirus 2, which causes corona virus disease 2019 (COVID-19), to help identify those who may need mechanical ventilation (MV). In this study, we aimed to determine if fibrosis-4 (FIB-4) is associated with the need for MV in patients with COVID-19 and if there is an association to determine the optimal FIB-4 cutoff. This was a retrospective, national, multiethnic cohort study of adults seen in an ambulatory or emergency department setting who were diagnosed with COVID-19. We used the TriNetX platform for analysis. Measures included demographics, comorbid diseases, and routine laboratory tests. A total of 4,901 patients with COVID-19 were included. Patients had a mean age of 56, 48% were women, 42% were obese, 38% were white, 40% were black, 15% had cardiac disease, 39% had diabetes mellitus, 20% had liver disease, and 50% had respiratory disease. The need for MV was 6%. The optimal FIB-4 cutoff for the need for MV was 3.04 (area under the curve, 0.735), which had sensitivity, specificity, and positive and negative predictive values of 42%, 77%, 11%, and 95%, respectively, with 93% accuracy. When stratified by race, increased FIB-4 remained associated with the need for MV in both white and black patients. *Conclusion:* FIB-4 can be used by frontline providers to identify patients that may require MV. (*Hepatology Communications* 2021;5:1605-1615).

Corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic leading to respiratory failure and the need for mechanical ventilation (MV).[1,2] While many are asymptomatic or have only mild symptoms, others present to emergency rooms and frontline providers with more severe symptoms.[3,4] Although the clinical course varies, observational studies have identified several comorbid conditions, such as diabetes mellitus, respiratory diseases, and obesity, in hospitalized patients that are linked to disease severity, including respiratory failure, a need for ventilator support, and mortality.[5-8] Therefore, there is interest in developing prediction tools to help in the early identification of patients infected with COVID-19 who might require more intensive monitoring and treatments.

Several complex models have been developed to predict mortality of hospitalized patients with COVID-19 by using clinical data and markers of increased inflammation associated with infection; however, few have focused on the need for MV, which is often a precursor to mortality.[2,9-14] One limitation of most of these models is the inclusion of nonroutine data; this makes their applicability to routine care challenging. To overcome these limitations, simple tests are needed. One simple test, increased red cell distribution width (RDW), was recently shown to be associated with increased mortality from COVID-19, but no data were provided on its association with MV.[15]

Infection with COVID-19 is associated with systemic inflammation and increased liver enzymes, which can be associated with poor prognosis regardless of preexisting liver disease.[14,16-19] The fibrosis-4 index (FIB-4), a simple index consisting of age, platelet (PLT) count, and two liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), was developed to predict advanced fibrosis in chronic liver disease. It has been hypothesized to be a surrogate for severity of the inflammatory response and to be associated with the need for MV and mortality in patients hospitalized with COVID-19.[7,20-22] However, because these studies were limited to single centers or unique populations and used established FIB-4 thresholds developed in viral hepatitis and nonalcoholic fatty liver disease (NAFLD), the utility of FIB-4 to help frontline providers identify who might be at higher risk for intensive care requires broad validation.[21,23] To address this gap in knowledge, our aims were 1) to determine if FIB-4 is associated with the need for MV in a national multiethnic cohort of patients seen for COVID-19 symptoms and 2) if an association exists, to determine the optimal FIB-4 cutoff associated with the need for MV.

Patients and Methods

DATA SOURCE

This was a retrospective analysis of a national multiethnic cohort of patients with COVID-19 in the United States, using the TriNetX platform (www.trinetx.com). We used the federated research network platform TriNetX (Supporting Appendix S1) to identify our initial cohort of 28,610 distinct patients with COVID-19 based on International Classification of Diseases, Tenth Revision (ICD-10) codes from the index visit or related hospitalizations. For the TriNetX platform, we queried all patients who had been

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diagnosed with either COVID-19 (U07.1) or pneumonia due to SARS-associated coronavirus (J12.81) between January and June 2020 in an ambulatory or emergency department setting. TriNetX does not allow data downloads or the review of individual patient data to assess when supplemental oxygen or MV occurred during the hospitalization. However, this platform allows analysis in the form of queries. TriNetX has previously been described in detail in several similar studies of COVID-19 that used this platform.[24-27] For all but 2 of these patients, we were able to identify the clinical encounter during which they were either diagnosed with COVID-19 or received a test for COVID-19 that yielded a positive result. Out of these encounters, we were able to identify 4,901 distinct patients who had recorded AST, ALT, and PLT values within the first 24 hours of the encounter that we could use to calculate a FIB-4 score. Because the data were de-identified, we were unable to obtain a reliable death date that could be used to assess 30-day mortality. Institutional review board approval was not required for the de-identified data.

Demographic data (age, sex, race/ethnicity), body mass index (BMI) if available, use of supplemental O_2, comorbid conditions (diabetes mellitus, cardiac disease, respiratory disease, and liver disease), and the need for intensive care unit (ICU) were identified by ICD-10 codes from the index visit or related hospitalizations (Supporting Table S1). The primary outcome, which was the need for MV, was identified by ICD-10 codes. AST, ALT, and PLT counts obtained from the day of the visit were used to determine the FIB-4 score, calculated as (age × AST) / (PLT × $ALT^{1/2}$).[20]

STATISTICAL ANALYSIS

Patient demographics (age, race, sex), comorbidities (cardiac, liver, respiratory, and diabetes), increased RDW (RDW >14.5%), obesity (BMI ≥30 kg/m^2), supplemental O_2 use, and FIB-4 (greater than or equal to the optimized cutoff) were analyzed as covariates. Data are presented as mean and SD for normally distributed data, median and interquartile range (IQR) for skewed continuous data, or frequency and percentage for categorical data, as appropriate. A multiple logistic regression model was used to estimate the impact of FIB-4 on the need for MV adjusted for covariates. We categorized age (ranging between 19 and 81 years) into four quartiles and analyzed their

effects on the need for MV because the categorical age produced a better fit than the continuous one. We first used the established FIB-4 cutoffs developed for advanced fibrosis in NAFLD and chronic hepatitis C to build on previous analyses that estimated the effect of binary FIB-4 dichotomized at ≥2.67 or ≥3.25 on the need for MV.[20,23] To determine our sample's optimal binary FIB-4 similar to how FIB-4 is used in chronic liver disease, we investigated the FIB-4 dichotomizing cutoffs between 2.50 and 4.00 and found the FIB-4 cutoff that maximized power to detect its effect on the need for MV. To assess the optimal cutoff against other cutoffs (2.67 and 3.25), we plotted the receiver operating characteristic (ROC) curve; obtained the area under the curve (AUC, also known as the C statistic), given the estimated multiple logistic regression model of interest with the binary FIB-4 based on each cutoff; and compared the resulting AUCs.

Each covariate was tested independently in a simple logistic regression model. Those that achieved a significance level with $P < 0.10$ were included as the predictors in a subsequent multiple logistic regression model of interest. The effects, odds ratios (ORs), and 95% confidence intervals (CIs) for the ORs were estimated by maximum likelihood for the need for MV (the primary outcome) and increased FIB-4 (a secondary outcome). The Hosmer-Lemeshow goodness-of-fit test was performed to assess the adequacy of the model.[28] Lastly, a 10-fold cross-validation was performed to evaluate the accuracy of the model. All statistical analyses were performed using R version 4.0 and SAS version 9.4.

Results

CHARACTERISTICS OF PATIENTS

Patient characteristics for the entire sample of 28,608 patients with COVID-19 and a subsample of 4,901 patients who had all the components to calculate FIB-4 at the time of evaluation are summarized in Table 1. The patients with FIB-4 data were more likely to be older, men, black, and obese; had a higher proportion with increased RDW, AST, and comorbid diseases; were more likely to use supplemental O_2; and were more likely to require ICU or MV than subjects who did not have the components to calculate FIB-4.

TABLE 1. CHARACTERISTICS OF THE COHORT

Variable		FIB-4 Patients (n = 4,901)	Entire Sample (n = 28,608)	Mean Difference (*P* Value)
Categorical variables: Proportion (%)				
Female (%)		48.45	54.69	−6.24 (<0.01)
Comorbid cardiac disease (%)		15.22	8.76	6.46 (<0.01)
Comorbid diabetes mellitus (%)		38.80	22.51	16.29 (<0.01)
Comorbid liver disease (%)		20.40	15.61	4.79 (<0.01)
Comorbid respiratory disease (%)		50.35	39.69	10.66 (<0.01)
Supplemental O_2 use (%)		3.71	1.12	2.58 (<0.01)
MV (%)		6.08	1.47	4.61 (<0.01)
ICU (%)		14.22	3.90	10.32 (<0.01)
Race (%)	American Indian or Alaska Native	0.45	0.33	391.32 (<0.01) chi-square test
	Asian	1.96	2.44	
	Black	39.58	26.13	
	Native Hawaiian or Pacific Islander	0.39	0.24	
	White	38.28	48.82	
	Unknown	19.34	22.04	
RDW (>14.5%) (%)		32.04 (17%)	29.68 (74%)	2.36 (<0.01)
Obesity (BMI, ≥30 kg/m^2) (%)		42.43 (78%)	38.48 (81%)	3.95 (0.02)
Continuous variables				
Age (years)*		55.74 (15.6, 0%)	48.32 (16.51, 0%)	7.42 (<0.01)
AST (U/L)[†]		37 (25-58, 0%)	34 (23-54, 89%)	3.76 (<0.01)
ALT (U/L)[†]		28 (18-47, 0%)	28 (18-47, 84%)	−1.79 (0.92)
(×1,000)[†]		220.0 (169-282, 0%)	217 (168-280, 73%)	3.08 (0.13)

* Mean (SD, %).
[†] Median (IQR, %).

NEED FOR MV

Of the 4,901 patients with FIB-4 data, 298 patients (6.08%) required MV. The difference in patient characteristics between patients who used the ventilator support and patients who did not during admission is compared in Table 2. Patients with ventilator support had a higher OR of being men and older; had more comorbid diseases; were obese; had higher FIB-4, AST, and use of supplemental O_2; and had lower PLT than those that did not require MV. However, the proportion with increased RDW and median ALT did not differ in means across the two groups of patients.

DETERMINING THE OPTIMAL FIB-4 CUTOFF

We found the optimal FIB-4 threshold associated with the need for MV at 3.04 among cutoffs ranging from 2.50 to 4.00 that maximized the power to detect the effect of FIB-4 on MV in a simple logistic regression model. To evaluate the optimal FIB-4 threshold 3.04 against other competing ones (2.67 and 3.25), we used the ROC curve of the estimated model in Table 3 to produce the ROC curve of each cutoff. Our threshold was one of the four FIB-4 cutoffs (2.91, 2.92, 3.03, and 3.04) that produced the maximum AUC of 0.7035. The analyzed cutoffs 2.67 and 3.25 noted in the literature produced comparative AUCs of 0.7014 and 0.7007, respectively (Fig. 1).[20,21] Therefore, the FIB-4 cutoff 3.04 not only achieved the maximum power to detect the FIB-4 effect but also produced the highest AUC among the competing dichotomizations of FIB-4. Using this cutoff, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 42%, 78%, 11%, and 95%, respectively. When setting the sensitivity or specificity at 90%, the cutoff FIB-4, PPV,

TABLE 2. FIB-4 PATIENTS WHO USED AND DID NOT USE VENTILATOR SUPPORT

Variable		Used MV (n = 298)	No MV (n = 4,603)	Mean Difference (*P* Value)
Categorical variables: Proportion (%)				
Female (%)		40.6	48.96	−8.36 (<0.01)
Comorbid cardiac disease (%)		25.5	14.55	10.95 (<0.01)
Comorbid diabetes mellitus (%)		59.73	37.45	22.28 (<0.01)
Comorbid liver disease (%)		27.51	19.94	7.57 (<0.01)
Comorbid respiratory disease (%)		67.11	49.27	17.84 (<0.01)
Supplemental O_2 use (%)		8.05	3.43	4.62 (<0.01)
ICU (%)		74.16	10.34	6.38 (<0.01)
Race (%)	American Indian or Alaska Native	0.67	0.43	6.92 (0.23) chi-square test
	Asian	2.35	1.93	
	Black	42.95	39.37	
	Native Hawaiian or Pacific Islander	0.67	0.37	
	White	31.54	38.71	
	Unknown	21.81	19.18	
FIB-4 ≥3.04) (%)		42.28	22.33	19.95 (<0.01)
RDW >14.5% (%)		36.92 (13%)	31.17 (17%)	5.21 (0.09)
Obesity (BMI ≥30 kg/m^2) (%)		54.61 (56%)	40.77 (79%)	13.84 (<0.01)
Continuous variables				
Age (years)*		58.96 (13.3, 0%)	55.53 (15.4, 0%)	3.43 (<0.01)
AST (U/L)[†]		45 (31-72, 0%)	36 (25-57, 0%)	65.54 (<0.01)
ALT (U/L)[†]		28.5 (19-46, 0%)	28 (18-47, 0%)	11.97 (0.73)
PLT (×1,000)[†]		199 (148-272, 0%)	221 (170-282, 0%)	−16.74 (<0.01)

*Mean (SD, %).
[†]Median (IQR, %).

and NPV were unchanged across the cutoffs (data not shown).

ANALYSIS OF INDEPENDENT ASSOCIATIONS WITH INCREASED FIB-4

Compared to those with FIB-4 <3.04 (n = 3,747), those with increased FIB-4 (≥3.04, n = 1,154) were more likely to be men (OR, 1.64; 95% CI, 1.43-1.92), black race (OR, 1.25; 95% CI, 1.07-1.45), had cardiac disease (OR, 40; 95% CI, 1.15-1.70), diabetes mellitus (OR, 1.18; 95% CI, 1.0-1.37), respiratory disease (OR, 1.30; 95% CI, 1.11-1.51), and used supplemental O_2 (OR, 2.10; 95% CI, 1.44-3.05). When only those with obesity recorded were assessed (n = 600), only men (OR, 1.75; 95% CI, 1.20-2.56) and black race (OR,

1.56; 95% CI, 1.07-2.56) were associated with increased FIB-4 while obesity itself was inversely related (OR, 0.62; 95% CI, 0.42-0.90). We found increased FIB-4 was more common in those with liver disease (23.65% vs. 19.40%; *P* < 0.01), but liver disease was not associated with increased FIB-4 when adjusting for demographics, obesity, and other chronic conditions.

ANALYSIS OF INDEPENDENT ASSOCIATIONS OF NEED FOR MV

We estimated the effects of sex, race, four comorbidities (cardiac disease, diabetes mellitus, liver disease, and respiratory disease), FIB-4 (≥3.04), supplemental O_2 use, and obesity on the MV outcome. We excluded RDW as insignificant and obesity severely missing for 79% of patients. Age, AST, ALT, and PLT were not included in the model due to the predictor FIB-4

TABLE 3. LOGISTIC REGRESSION ANALYSIS OUTCOME OF PATIENTS WITH FIB-4 ON THE NEED FOR MV

Variables		Simple Logistic Regression (n = 4,901)			Multiple Logistic Regression (n = 3,953)*			Multiple Logistic Regression (n = 774)†		
		Estimates (P Value)	OR	95% CI	Estimates (P Value)	OR	95% CI	Estimates (P Value)	OR	95% CI
Intercept		-	-	-	−3.84 (<0.01)			−3.29 (<0.01)		
Female		−0.34 (<0.01)	0.71	0.56-0.90	−0.26 (0.07)	0.77	0.58-1.02	−0.22 (0.35)	0.80	0.50-1.27
Age group (Ref. ≤33)	(34, 48)	0.75 (0.02)	2.12	1.14-3.94						
	(49, 60)	1.02 (<0.01)	2.76	1.52-5.01						
	(≥61)	1.11 (<0.01)	3.00	1.70-5.38						
Race (ref. white)	Native American	0.64 (0.39)	1.89	0.43-8.23	0.56 (0.46)	1.76	0.39-7.88	1.16 (0.33)	3.19	0.30-33.1
	Asian	0.40 (0.32)	1.49	0.67-3.30	0.52 (0.21)	1.68	0.74-3.84	-0.24 (0.76)	0.78	0.17-3.61
	Black	0.29 (0.04)	1.34	1.01-1.76	0.31 (0.03)	1.36	1.02-1.81	0.47 (0.04)	1.60	1.01-2.53
	Native Hawaiian	0.80 (0.29)	2.23	0.51-9.79	0.96 (0.21)	2.63	0.58-11.9	1.68 (0.05)	5.4	0.95-30.5
	Unknown	0.33 (0.05)	1.40	1.00-1.93						
Supplemental O$_2$		0.90 (<0.01)	2.46	1.57-3.85	0.52 (0.06)	1.68	0.96-2.94	0.33 (0.33)	1.40	0.71-2.77
Comorbidity Cardiac disease		0.70 (<0.01)	2.01	1.53-2.64	0.34 (0.04)	1.40	1.01-1.94	0.28 (0.27)	1.33	0.80-2.21
Comorbidity diabetes mellitus		0.91 (<0.01)	2.47	1.95-3.14	0.53 (<0.01)	1.69	1.28-2.24	0.56 (0.02)	1.75	1.09-2.81
Comorbidity liver disease		0.42 (<0.01)	1.52	1.17-1.98	0.33 (0.03)	1.39	1.02-1.91	0.71 (<0.01)	2.03	1.25-3.29
Comorbidity respiratory disease		0.74 (<0.01)	2.10	1.63-2.69	0.38 (0.01)	1.47	1.88-1.98	0.11 (0.69)	1.11	0.65-1.89
AST		2.3e-4 (0.02)	1.00	1.00-1.00						
ALT		5.5e-4 (0.10)	1.00	1.00-1.00						
		−1.8e-3 (<0.01)	1.00	1.00-1.00						
FIB-4 ≥3.04		0.94 (<0.01)	2.55	2.00-3.24	0.92 (<0.01)	2.52	1.92-3.32	0.79 (<0.01)	2.20	1.40-3.46
BMI ≥30 kg/m² (missing in 80%)		0.56 (<0.01)	1.75	1.21-2.52	-	-	-	0.41 (0.08)	1.51	0.96-2.37
RDW >14.5%		0.23 (0.08)	1.26	0.97-1.64						

P < 0.05 indicates significant association in multivariate analysis.
*Includes patients with all available data not including BMI.
†Includes only those with BMI data.

defined as a function of them. In addition, patients with unknown or missing race were excluded.

The associations with the need for MV in the cohort with these adjustments are shown in Table 3. In those patients with all available data (n = 3,953) after controlling for other covariates, positive associations with the need for MV were black race (OR, 1.36; 95% CI, 1.02-1.81), cardiac disease (OR, 1.40; 95% CI, 1.01-1.94), diabetes mellitus (OR, 1.69; 95% CI, 1.28-2.24), respiratory disease (OR, 1.47; 95% CI, 1.88-1.98), liver disease (OR, 1.39; 95% CI, 1.02-1.91), and patients with FIB-4 ≥3.04. These patients were more likely to use ventilator support than other patients (OR, 2.52; 95% CI, 1.92-3.32). The goodness-of-fit test implied that the final model was adequate with *P* = 0.31. Lastly, our predictive model achieved 93% accuracy in predicting the response by 10-fold cross validation. When data were restricted to

those with obesity data (n = 774), along with underlying liver disease, black race, diabetes, and FIB-4 remained associated with the need for MV (Table 3) while obesity, respiratory disease, and cardiac disease did not have this association.
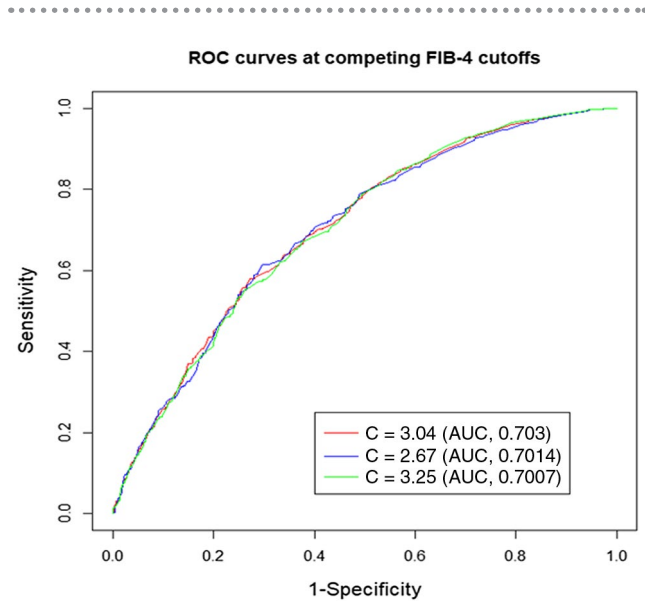

FIG. 1. Area under the receiver operating characteristic curve at competing FIB-4 cutoffs.

IMPACT OF RACE ON NEED FOR MV

When we compared the entire cohort stratified by race (white, n = 1,876; black, n = 1,940; and others, n = 1,085, which included Asian, Native American, Pacific Islander, and a large proportion of unknowns), diabetes mellitus and respiratory disease remained independently associated with the need for MV across all races (Table 4) while supplemental O_2 and liver diseases were significant only among whites and cardiac disease only among blacks. Importantly, increased FIB-4 remained associated with the need for MV in both whites (OR, 2.1; 95% CI, 1.3-3.2) and blacks (OR, 3.1; 95% CI, 2.2-4.5) but not in others or those of unknown race.

Discussion

A major challenge for frontline providers is predicting which patients with COVID-19 will progress to respiratory failure and the need for MV. In this national multiethnic cohort of patients with COVID-19, we observed a need for MV of 6.08%, which is similar to other studies, and confirm the independent association of increased FIB-4, a simple

TABLE 4. LOGISTIC REGRESSION ANALYSIS OUTCOME OF PATIENTS WITH FIB-4 ON THE NEED FOR MV BY RACE

Variables	Entire Sample (n = 4,901)		White (n = 1,876)		Black (n = 1,940)		Others (n = 1,085)	
	Estimate (*P* Value)	Odds (CI)	Estimate (*P* Value)	Odds (CI)	Estimate (*P* Value)	Odds (CI)	Estimate (*P* Value)	Odds (CI)
Intercept	−3.58 (<0.01)		−3.82 (<0.01)		−3.79 (<0.01)		−3.22 (<0.01)	
Female	−0.22 (0.08)	0.80 (0.6- 1.0)	−0.54 (0.02)	0.58 (0.3- 0.9)	0.04 (0.81)	1.04 (0.7- 1.5)	−0.3 (0.15)	0.70 (0.4- 1.1)
Supplemental O_2	0.52 (0.03)	1.68 (1.1-2.7)	0.74 (0.03)	2.1 (1.1- 4.2)	0.39 (0.43)	1.48 (0.5- 3.9)	0.17 (0.68)	1.2 (0.5- 2.8)
Comorbidity cardiac disease	0.19 (0.21)	1.2 (0.9-1.6)	0.17 (0.49)	1.2 (0.7- 1.9)	0.49 (0.03)	1.63 (1.1- 2.5)	−0.35 (0.41)	0.7 (0.3- 1.6)
Comorbidity diabetes mellitus	0.68 (<0.01)	1.9 (1.5-2.5)	0.53 (0.02)	1.7 (1.1- 2.7)	0.55 (<0.01)	1.73 (1.2- 2.5)	1.02 (<0.01)	2.8 (1.7- 4.7)
Comorbidity liver disease	0.15 (0.30)	1.2 (0.8- 1.5)	0.57 (0.02)	1.7 (1.1- 2.8)	0.16 (0.48)	1.2 (0.8- 1.8)	−0.57 (0.17)	0.56 (0.2- 1.3)
Comorbidity respiratory disease	0.46 (<0.01)	1.6 (1.2-2.1)	0.52 (0.04)	1.7 (1.0- 2.8)	0.40 (0.05)	1.5 (1.0- 2.2)	0.66 (<0.01)	1.94 (1.2- 3.2)
(FIB-4 ≥3.04)	0.76 (<0.01)	2.14 (1.7- 2.7)	0.74 (<0.01)	2.1 (1.3- 3.2)	1.14 (<0.01)	3.1 (2.2- 4.5)	0.006 (0.98)	1.00 (0.5- 1.8)

P < 0.05 indicates a significant association.
Entire cohort comprised white, black, others, and unknown. Others comprised Asian, Native American, Pacific Islander, and unknown.

index that includes routine data, with the need for MV during hospitalization.[19] When controlling for comorbid diseases, including liver disease, FIB-4 remained associated with the need for MV across racial groups.

Recent studies have modeled associated factors with increased morbidity associated with COVID-19. Knight and colleagues[12] looked at over 35,000 patients admitted to hospitals across England, Scotland, and Wales to develop the 4C mortality score, which includes eight variables (age, sex, number of comorbidities, respiratory rate peripheral oxygen saturation, level of consciousness, urea, and C-reactive protein [CRP]). The 4C mortality score had an AUC of 0.79. More recently, the BAS^{2}IC score was developed, which includes age, sex, BMI, dyspnea, CRP, and lymphocyte count; this score had an AUC of 0.76, which is in line with other scores to predict mortality in COVID-19.[13] However, these models are complex and include subjective symptoms (dyspnea) and nonroutine laboratory tests (CRP), limiting their utility in clinical practice.[10,29-45]

Simple models of routine data have the advantage over more complex models because of their ease of use. FIB-4 was developed and cutoffs determined to predict advanced liver fibrosis; this score has been validated in those with viral hepatitis and NAFLD.[20,23,46] Studies in patients with diabetes mellitus and in patients with NAFLD found increased FIB-4 associated with increased mortality from COVID-19.[6,7] However, it is unclear if these studies represent the severity of COVID-19 or underlying liver disease. In a recent study of 287 hospitalized Veterans with COVID-19 after adjusting for comorbid diseases, FIB-4 >3.25 had an OR of 8.40 for ICU admission compared to FIB-4 <1.45.[22] However, because over 50% of the cohort had an indeterminate FIB-4 value (1.45-3.25), the applicability using this cutoff was limited. Similar to our findings in an unselected national multiethnic population, other studies found increased FIB-4 (>2.67) to be associated with SARS-CoV-2 infection severity.[21,47]

While other studies used published FIB-4 thresholds in viral hepatitis (>3.25) and NAFLD (>2.67), we were able to determine that the optimal FIB-4 threshold associated with the need for MV was 3.04, which is between the threshold used to identify advanced fibrosis in NAFLD and chronic hepatitis C.[20,23,46] Increased FIB-4 in our cohort was associated with

male sex, black race, supplemental O_2, diabetes, and cardiac and respiratory disease; it was not associated with a history of liver disease, and similar to the single-center study by Sterling and colleagues,[21] it was inversely associated with obesity in our national multiethnic cohort.

Of the components of FIB-4, we observed increased age, increased AST, and lower PLT count were all associated with MV by analysis of simple logistic regression models; this reflects the systemic inflammation associated with COVID-19.[14,16-19] The association of increased AST to ICU admission and the need for MV has been reported.[5,19,47,48] However, when individually substituted with FIB-4 in our multiple regression model, AST, ALT, and PLT count were not independently associated with the need for MV, confirming it is the FIB-4 index and not its components that are associated with disease severity.[21] Although a recent study found that increased RDW, a standard component of the complete blood count, was associated with increased mortality among hospitalized patients with COVID-19, we did not observe an impact of increased RDW on MV, which is often a precursor to mortality.[15]

The impact of race on COVID-19 severity is controversial. Despite a prevalence of 13% in the black race in the United States compared to the white race (76%), we found a similar prevalence (39%) in both races in our cohort of patients with COVID-19.[49] Although other studies have had mixed results on the impact of race on disease severity, we observed that black patients had a higher rate in the need for MV than white patients.[19,21,22,50] We did not observe an impact of obesity on COVID-19 severity, but other studies have,[7,21,47] and similar to others, we observed an impact of diabetes mellitus on COVID-19 severity.[5,21] Interestingly, when obesity was included in the model, both cardiac and respiratory diseases were no longer significantly associated with the need for MV but liver disease and diabetes were.

Increased FIB-4 may not be assessing liver fibrosis, but it most likely reflects a more global score of systemic inflammation associated with COVID-19.[14,16,18,47] We observed increased FIB-4 in those with a history of diabetes, cardiac disease, and respiratory disease but surprisingly not with liver disease. In support of the independent association of FIB-4 to non-liver related outcomes, increased FIB-4 was associated with outcomes in patients with intracranial hemorrhage while

the NAFLD fibrosis score was not, suggesting that it has unique properties separate from liver disease.[48]

The strengths of our study are the large sample size and racial diversity reflective of the national cohort. However, our study also has several limitations. Our data and outcomes were determined by a de-identified data set obtained by TriNetX from January to June 2020 and may be subject to temporal bias. Therefore, comorbid conditions that were not properly recorded may have affected our data. While race was recorded in a large proportion of our cohort, the substantial number listed as "unknown" may have limited our ability to assess the utility of FIB-4 stratified by race and specifically in Hispanics. Similarly, we did not have data to determine obesity (height and weight) in a majority of subjects. In addition, we did not have historical data to assess if increased liver enzymes or low PLTs were new and related to the COVID-19 infection or chronic and due to a prior diagnosed or unrecognized chronic liver disease. We also were unable to capture reliable data on prior viral hepatitis infection or alcohol use, which may have affected our ability to diagnose known history and impact of liver disease. Although we did capture supplemental oxygen use, we were not able to differentiate between the need for high and low flow oxygen or when supplemental oxygen was used during hospitalization. Furthermore, we were not able to capture data on mortality. Because we used a de-identified national data set, we were also not able to determine the exact time (hour or days) from admission to the need for MV, and therefore we were not able to determine if FIB-4 was a better predictor of early or late respiratory disease associated with COVID-19. The differences in comorbidities between patients without the components to calculate FIB-4 (Table 1) most likely reflect a less severe COVID-19 clinical presentation. Therefore, we did not compare the need for MV between these two cohorts. Furthermore, we did not have the data to calculate several more complex models (4C mortality score and BAS^{2}IC score) for comparison to FIB-4. Lastly, we did not include any experimental treatments that patients could have received for COVID-19, which may have impacted the utility of FIB-4 on admission to eventual need for MV during hospitalization.

In conclusion, FIB-4, a simple clinical index of readily available clinical data measured at presentation, can be used by frontline providers to help identify which patients, regardless of race, may require more intensive care and MV. With the need for MV in our cohort of 6%, similar to published reports, we found FIB-4 to have a very high NPV with moderate specificity, suggesting the real utility of FIB-4 may be in identifying those who may not (ruling out) rather than those who will (ruling in) need MV.[19] While FIB-4 may not be measuring hepatic fibrosis, those with increased FIB-4 are more than twice as likely to require MV.

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