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ORIGINAL ARTICLE

Comparison of liver fibrosis scores and fatty liver on computed tomography as risk factors for severity of COVID-19

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Abstract

Background and Aim: Increased liver fibrosis scores (LFS), such as fibrosis-4 index (FIB-4) or non-alcoholic fatty liver disease fibrosis score (NFS), and fatty liver are known risk factors for severe coronavirus disease 2019 (COVID-19). The purpose of this study was to identify the best scores, which predict the prognosis of COVID-19.
Methods: Participants comprised consecutive Japanese COVID-19 patients admitted to our hospital between February 14, 2020, and April 14, 2021. Multivariate logistic regression analysis was performed to evaluate the relationships between LFS (FIB-4, NFS, aspartate aminotransferase-to-platelet ratio index [APRI], BARD score, and hepatic steatosis index [HSI]) or fatty liver on computed tomography (CT), and severity of COVID-19.
Results: Of the 415 patients (mean age, 59 years), 177 patients (42.7%) needed oxygen therapy, 90 patients (21.7%) worsened to severe COVID-19, and 45 patients (10.8%) died during admission. Multivariate logistic regression analysis showed that increased FIB-4 and NFS were risk factors for death, severe COVID-19, and oxygen demand; that increased BARD was a risk factor for severe COVID-19 and oxygen demand; and that increased APRI and HSI were not risk factors for any status of COVID-19. Furthermore, increased NFS or BARD and fatty liver were independent risk factors for severe COVID-19 and oxygen demand.
Conclusions: This study showed that FIB-4 and NFS were the best liver fibrosis scores that predicted worse prognosis for COVID-19, and that increased NFS or BARD and fatty liver evident on CT represented independent risk factors for severe COVID-19 and oxygen demand.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and since its emergence in December 2019, it has infected 771.8 million people worldwide, with 6.98 million deaths as of November 8, 2023.[1] COVID-19 is characterized by pneumonia, with a unique appearance on computed tomography (CT) and a wide spectrum of clinical severity.[2]

Many studies have attempted to elucidate risk factors for COVID-19 severity and fatality. In many case series, older patients[3] and patients with hypertension, diabetes mellitus (DM), or cardiovascular diseases[2,4] were more likely to develop acute respiratory distress syndrome and require mechanical ventilation. Ji et al. identified non-alcoholic fatty liver disease (NAFLD) was up to 38% of patients with COVID-19,[5] and the presence of NAFLD had been associated with worse prognosis.[5,6]

Hepatic fibrosis is an early histological change before the development of cirrhosis, which is the end sequela in many liver diseases (e.g., hepatitis B or hepatitis C virus infection, chronic alcoholism, and NAFLD).[7] Noninvasive liver fibrosis scores (e.g., fibrosis-4 index [FIB-4],[8,9] NAFLD fibrosis score [NFS],[10] aspartate aminotransferase-to-platelet ratio index [APRI],[11] BARD score,[12] and hepatic steatosis index [HSI][13]) have been developed to screen the extent of liver fibrosis in chronic liver disease.[14]

These scores have also been validated for use as prognostic indicators for NAFLD.[15–17] Recently, hepatic dysfunction elevated with the FIB-4 at admission on acute heart failure (AHF) was revealed to be a predictor of the composite endpoint of all-cause mortality and rehospitalization in AHF group.[18] Also, Cao YX reported that elevated liver fibrosis scores (FIB-4, NFS and BARD) could be used as a risk stratification tool for predicting cardiovascular outcomes in patients with previous myocardial

infarction.[19] Moreover, the liver fibrosis scores used to assess advanced fibrosis (FIB-4 NFS, APRI, BARD and HSI) also correlate with increased risks for mechanical ventilation (MV), intensive care, and mortality of COVID-19.[20–25] However, the results have been inconsistent.[26–28]

Several studies have reported a relationship between COVID-19 and fatty liver on CT.[29–31] Fatty liver on admission CT has been revealed as a risk factor for severe COVID-19 requiring oxygen therapy.[32]

Nevertheless, little is known about the relationships between FIB-4, NFS, BARD, APRI, HSI, and fatty liver on CT in terms of the risk of severe COVID-19.

The purpose of this study was to clarify that these liver fibrosis scores and fatty liver on CT, which were considered to be the prognostic factor, could also be the prognostic factor for severity of COVID-19, and to identify the best scores that predict the prognosis of COVID-19.

Methods

Ethics. This study was approved by the institutional review board (approval no. 20-A-06). The need to obtain written informed consent was waived due to the retrospective nature of the investigation. This study was performed in accordance with the provisions of the Declaration of Helsinki.

Study design and participants

Inclusion criteria. In this retrospective cohort study, consecutive COVID-19 patients diagnosed and admitted to our institution between February 14, 2020, and April 14, 2021 (the day before the first SARS-CoV-2 variant was detected in our hospital) were included for analysis. SARS-CoV-2 infection was diagnosed based on a positive result from real-time reverse transcription polymerase chain reaction testing or loop-mediated isothermal amplification testing of nasopharyngeal-swab specimens.

Exclusion criteria. Patients who were younger than 16 years old, non-Japanese, asymptomatic, admitted more than 14 days after onset of COVID-19 symptoms, or who received hyperalimentation or tube feeding were excluded.

Data collection and definitions

Data collection. We collected data from the electronic medical records of patients, including age, sex, vital signs, comorbidities (cardiovascular diseases, cerebrovascular diseases, hypertension, DM, respiratory disorders [chronic lung disease], chronic renal failure [chronic kidney disease], malignancy [cancer]), symptoms, laboratory findings, presence of pneumonia on chest radiography or CT, treatment modality, and hospitalization outcomes. The normal ranges for laboratory data were based on institutional standards.

Plain CT acquisition and interpretation. Plain CT examinations were performed from the chest to the upper abdomen, using one of three multidetector-row CT (MDCT) systems on the day of patient admission to the hospital: a 320-MDCT system (Aquilion ONE; Canon Medical Systems, Otawara, Tochigi, Japan); a 64-MDCT system (Revolution MAXIMA; GE Healthcare, Chicago, IL, USA); or an 80-MDCT system (Aquilion Prime SP; Canon Medical Systems). Section thickness was 3 mm, and scan parameters were 120 kVp, with automatically set mAs values. In visual analysis, liver steatosis was evaluated as follows: (i) no fatty liver, hepatic vessels showing lower attenuation than liver parenchyma; (ii) mild, hepatic vessels showing lower attenuation than liver parenchyma, but blurred contours; (iii) moderate, hepatic vessels showing the same attenuation as liver parenchyma; or (iv) severe, hepatic vessels showing higher attenuation than liver parenchyma.[32,33]

Definitions of variables. Based on the Japanese National COVID-19 guidelines,[34] we divided COVID-19 patients into four categories of severity: (i) asymptomatic; (ii) mild, with symptoms but no respiratory failure; (iii) moderate, with respiratory failure but not requiring oxygen therapy or requiring oxygen only via either nasal cannula or facial mask; or (iv) severe, requiring high-flow nasal cannula oxygen therapy, noninvasive ventilatory support, or invasive mechanical ventilatory support. If the condition of the patient worsened after admission, the most severe category applicable was used. Moderate or severe fatty liver on CT was defined as fatty liver on CT. Liver fibrosis scores obtained at the time of hospital admission were calculated using the following formulas: FIB-4 index = [age × aspartate aminotransferase (AST) level (IU/L)]/[platelet count ($\times 10^9$/L)] × [√alanine transaminase (ALT) level (IU/L)]; NAFLD fibrosis score = $-1.675 + 0.037 \times$ age (years) $+0.094 \times$ body mass index (BMI) (kg/m^2) $+1.13 \times$ DM (yes = 1, no = 0) $+0.99 \times$ AST [U/L]/ALT [U/L]—$0.013 \times$ platelet count ($\times 10^9$/L)—$0.66 \times$ albumin (g/dL); APRI = AST level (/upper limit of normal range) × 100/platelet count ($\times 10^9$/L); BARD = [sum of (**B**MI ≥ 28 kg/m^2 = 1 point; AST/ALT ratio ≥0.8 = 2 points; **D**M = 1 point)], HSI = 8 × (ALT/AST) + body mass index (BMI) + (2, if DM) + (2, if female). For calculating the NFS, BARD, and HSI, we defined DM as a known history of DM or glucose level on admission ≥200 mg/dL or hemoglobin (Hb) A1c on admission ≥6.5%.

Statistical analysis. Continuous and binary/categorical variables of baseline characteristics for COVID-19 patients are presented as mean (standard deviation [SD]) and number (proportion), respectively. Categorical variables were compared between groups using the χ^2 test.

A logistic regression model was used to identify risk factors for each outcome. First, simple logistic regression analyses were performed for each variable in COVID-19 patients, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Candidate predictors showing a P-value <0.1 on simple logistic regression analyses were included and evaluated in a multivariate logistic regression analysis to identify independent risk factors.

If a fibrosis score was identified as an independent risk factor for an outcome in the multivariate logistic regression analysis, thresholds for that fibrosis score were estimated based on the Youden index for the outcome. The receiver operating characteristic (ROC) curve was made based on the estimated thresholds. We compared the area under the receiver operating characteristic curve (ROC-AUC) using the DeLong test for each outcome.[35] Sensitivity, specificity, positive predictive value, and

Table 1 Baseline characteristics of the cohort

Background characteristics			
	COVID-19 ($n = 415$)	Missing data	Logistic regression
Age, years	59 (20)	0	
Age > = 65 years	181 (43.6%)	0	●
Gender Male	244 (58.8%)	0	●
BMI, kg/m^2	24.8 (16.1)	28	
BMI > = 25 kg/m^2	129 (33.4%)	28	●
Cardiovascular diseases	47 (11.3%)	0	●
Cerebrovascular diseases	36 (8.7%)	0	●
Hypertension	149 (35.9%)	0	●
Diabetes mellitus	81 (19.5%)	0	●
Respiratory disorders (Chronic lung disease)	56 (13.5%)	0	●
Chronic renal failure (Chronic kidney disease)	19 (4.6%)	0	●
Malignancy (Cancer)	27 (6.5%)	0	●
Albumin, g/dL	3.8 (0.6)	1	●
AST, IU/L	38 (31)	0	●
ALT, IU/L	33 (40)	0	●
LDH, IU/L	259 (111)	1	
BUN, mg/dL	17.7 (12.2)	0	
eGFR, mL/min/1.73m^2	69.31 (25.55)	0	
eGFR <= 60 mL/min/1.73m^2	138 (33.3%)	0	●
First visit glucose, mg/dL	134 (62)	4	
Admission glucose, mg/dL	132 (60)	4	
Hemoglobin A1c, %	6.2 (1.4)	63	●
C-reactive protein, mg/dL	4.73 (6.01)	0	
White blood cell count (Leukocyte), 10^3/mL	5553 (2894)	0	
Neutrophil count, 10^3/mL	4075 (2773)	1	
Lymphocyte count, 10^3/mL	1071 (521)	1	
Lymphocyte count <= 10^3/mL	214 (51.7%)	1	●
Platelet count 10^3/mL	20.6 (7.2)	0	●
Fibrinogen, mg/L	447 (139)	7	
D-dimer, mg/L	1.8 (5.2)	3	
D-dimer > = 1 mg/dL	140 (34.0%)	3	●
FIB-4 Index	2.51 (2.62)	0	●
NFS	1.62 (2.17)	4	●
APRI	0.58 (0.67)	0	●
BARD	2.15 (0.89)	0	●
BARD 0	29 (7.0%)	0	
BARD 1	28 (6.8%)		
BARD 2	233 (56.1%)		
BARD 3	102 (24.6%)		
BARD 4	23 (5.5%)		
HSI	37.3 (16.6)	28	●
Fatty Liver	135 (32.6%)	1	●
Outcomes			
Death	45 (10.8%)	0	
Severe COVID-19	90 (21.7%)	0	
Oxygen demand	177 (42.7%)	0	
Pneumonia	356 (85.8%)	0	
Days from onset to admission	5 (3)	0	
Admission period	18 (22)	0	

Unless otherwise stated, data are presented as *n* (%) for categorical data and mean (standard deviation) for continuous data.

●, variables used for logistic regression analyses; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; LDH, lactate dehydrogenase; NFS, non-alcoholic fatty liver disease fibrosis score.

negative predictive value were calculated in the fibrotic score with the highest discrimination ability for each outcome. To calculate the positive and negative predictive value, we regarded the prevalence of death, severe COVID-19, and oxygen demand in this study as that in the population, because all patients diagnosed with COVID-19 were admitted to the hospital based on the policy in Japan during the study period.

In addition, if fatty liver was included in the multivariate logistic regression for each outcome, fibrosis scores were managed as binary data based on the estimated thresholds, and interaction terms were constructed between fibrosis scores and the absence/presence of fatty liver. The interaction between these factors was then investigated in multivariate logistic regression models.

A two-sided *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Tochigi, Japan[36]), a modified version of R Commander, and STATA® version 16 (Stata Corp, College Station, TX).

Results

Study flow diagram and patient characteristics. During the study period, 458 patients with laboratory-detected SARS-CoV-2 infection in Tokyo Shinagawa Hospital, Japan, were enrolled. Among these patients, we excluded 6 patients who were non-Japanese, 15 patients who were asymptomatic, 20 patients who were admitted >14 days after the onset of COVID-19, and 2 patients who received hyperalimentation or tube feeding. As a result, data from 415 Japanese patients were analyzed.

Table 1 shows the baseline characteristics of the cohort. The mean age of the cohort was 59 years, and 244 patients (58.8%) were male. The most common comorbidity was hypertension ($n = 149$ [combined total], 35.9%), followed by DM ($n = 81$, 19.5%), respiratory disorders (chronic lung disease) ($n = 56$, 13.4%), and cardiovascular diseases ($n = 47$, 11.3%).

Among the 415 patients, 117 patients (42.7%) received oxygen therapy, 90 patients (21.7%) worsened to severe COVID-19, and 45 patients (10.8%) died.

Risk factors for death. Simple logistic regression analyses for death, severe COVID-19, and oxygen demand showed that age ≥ 65 years old, cardiovascular disease, hypertension, DM, DM + admission glucose ≥200 mg/dL + HbA1c ≥ 6.5%, albumin, AST, eGFR ≤60 mL/min/1.73 m^2, C-reactive protein, lymphocyte count ≤10^3/mL, D-dimer ≥1 mg/dL, platelet count, NFS,

Table 2 Simple logistic regression analyses for death, severe disease, and oxygen demand

	Death			Severe COVID-19			Oxygen demand		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age > = 65 years	10.44	4.31–25.28	<0.001	2.98	1.83–4.84	<0.001	4.22	2.79–6.39	<0.001
Gender Male	1.46	0.76–2.80	0.258	2.12	1.27–3.53	0.004	1.78	1.19–2.66	0.005
BMI > = 25 kg/m^2	1.24	0.61–2.50	0.550	3.64	2.18–6.05	<0.001	2.71	1.76–4.19	<0.001
Cardiovascular diseases	6.88	3.39–13.98	<0.001	4.77	2.54–8.97	<0.001	3.28	1.72–6.27	<0.001
Cerebrovascular diseases	4.46	2.02–9.86	<0.001	2.54	1.24–5.19	0.011	1.77	0.89–3.52	0.105
Hypertension	3.39	1.79–6.43	<0.001	3.86	2.37–6.28	<0.001	4.14	2.70–6.33	<0.001
Diabetes mellitus	2.59	1.33–5.04	0.005	6.28	1.97–5.66	<0.001	4.24	2.50–7.17	<0.001
Diabetes mellitus + admission glucose > = 200 mg/dL + HbA1c > = 6.5%	2.41	1.27–4.57	0.007	3.14	2.08–5.61	<0.001	4.52	2.80–7.29	<0.001
Respiratory disorders (Chronic lung disease)	4.57	0.78–3.79	0.180	2.08	1.13–3.84	0.019	1.97	1.11–3.48	0.020
Malignancy (Cancer)	1.98	0.71–5.51	0.192	1.29	0.53–3.15	0.581	2.05	0.93–4.54	0.076
Albumin, g/dL	0.23	0.13–0.40	<0.001	0.25	0.16–0.39	<0.001	0.23	0.15–0.35	<0.001
AST, IU/L	1.01	1.00–1.02	0.048	1.01	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001
ALT, IU/L	0.99	0.97–1.00	0.089	1.00	1.00–1.01	0.687	1.01	1.00–1.01	0.086
eGFR <= 60 mL/min/1.73m^2	7.91	3.86–16.19	<0.001	4.04	2.48–6.58	<0.001	3.90	2.54–6.00	<0.001
C-reactive protein, mg/dL	1.08	1.04–1.12	<0.001	1.15	1.10–1.20	<0.001	1.23	1.17–1.30	<0.001
Lymphocyte count <= 10^3/mL	2.44	1.24–4.80	0.010	2.61	1.58–4.32	<0.001	2.33	1.56–3.48	<0.001
Platelet count 10^3/mL	0.92	0.87–0.97	0.003	0.95	0.91–0.99	0.006	0.97	0.94–1.00	0.042
D-dimer > = 1 mg/dL	5.90	2.98–11.68	<0.001	2.77	1.71–4.48	<0.001	2.93	1.93–4.47	<0.001
NFS	1.46	1.20–1.78	<0.001	1.61	1.37–1.90	<0.001	1.78	1.53–2.06	<0.001
FIB-4	1.31	1.18–1.46	<0.001	1.28	1.15–1.41	<0.001	1.40	1.23–1.59	<0.001
BARD	2.22	1.49–3.30	<0.001	2.69	1.93–3.75	<0.001	3.97	1.73–2.99	<0.001
APRI	1.52	1.07–2.17	0.020	1.85	1.27–2.69	0.001	2.06	1.35–3.13	0.001
HSI	1.01	0.99–1.02	0.350	1.02	0.99–1.05	0.265	1.03	1.00–1.07	0.069
Fatty liver	1.44	0.76–2.71	0.264	2.69	1.61–4.20	<0.001	2.61	1.71–3.97	<0.001

ALT alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; FIB-4, fibrosis-4 index; HbA1c, hemoglobin A1c; HSI, hepatic steatosis index; NFS, non-alcoholic fatty liver disease fibrosis score.

Table 3 Multivariate logistic regression analysis of death

	Model 1			Model 2 (FIB-4)			Model 3 (NSF)			Model 4 (BARD)			Model 5 (APRI)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age > = 65 years	3.15	1.10–9.00	0.032							3.24	1.13–9.31	0.029	3.14	1.10 –8.97	0.033
Cardiovascular diseases	2.12	0.87–5.16	0.098	2.30	0.95–5.58	0.066	3.34	1.48–7.55	0.004	2.04	0.85 –4.88	0.108	2.19	0.90 –5.28	0.082
Cerebrovascular diseases	2.15	0.82–5.64	0.121	2.08	0.81–5.34	0.128	2.37	0.50–6.05	0.071	1.98	0.74 –5.25	0.171	2.15	0.82 –5.65	0.120
Hypertension	0.95	0.42–2.16	0.911	1.06	0.47–2.36	0.890	1.07	0.50–2.30	0.869	0.90	0.40 –2.02	0.795	0.95	0.42 –2.15	0.907
Diabetes Mellitus	1.72	0.21–0.74	0.206	1.62	0.70–3.75	0.255							1.70	0.74 –3.94	0.212
Albumin, g/dL	0.63	0.29–1.38	0.247	0.59	0.28–1.24	0.163				0.69	0.31 –1.53	0.357	0.63	0.28 –1.38	0.246
AST, IU/L	1.00	0.99–1.01	0.946												
eGFR <= 60 mL/min/1.73m^2	3.49	1.54–7.90	0.003	3.82	1.70–8.59	0.001	3.96	1.78–8.81	0.001	3.44	1.52 –7.80	0.003	3.47	1.54 –7.84	0.003
C-reactive protein, mg/dL	1.02	0.96–1.07	0.559	1.00	0.95–1.06	0.890	1.02	0.97–1.08	0.348	1.01	0.96 –1.07	0.594	1.02	0.96 –1.08	0.512
Lymphocyte count <= 10^3/mL	1.16	0.51–2.61	0.720	1.36	0.61–3.03	0.456	1.34	0.61–2.97	0.467	1.21	0.53 –2.72	0.651	1.14	0.50 –2.57	0.758
Platelet count 10^3/mL	0.92	0.87–0.98	0.010							0.92	0.87 –0.98	0.01	0.92	0.86 –0.98	0.014
D-dimer > = 1 mg/dL	1.79	0.75–4.27	0.191	1.84	0.80–4.24	0.151	2.22	1.01–4.89	0.047	1.82	0.77 –4.32	0.175	1.82	0.77 –4.34	0.174
FIB-4				1.14	1.02–1.27	0.017									
NFS							1.15	1.01–1.30	0.038						
BARD										1.63	0.97 –2.73	0.064			
APRI													0.88	0.49 –1.57	0.655

AST, aspartate aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

Table 4 Multivariate logistic regression analysis of severe COVID-19

	Model 1			Model 2 (FIB-4)			Model 3 (NSF)			Model 4 (BARD)			Model 5 (APRI)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age > = 65 years	1.48	0.64–3.45	0.358							1.22	0.56–2.64	0.612	1.50	0.65–3.48	0.345
Gender Male	1.55	0.77–3.15	0.220	1.63	0.82–3.26	0.164	1.88	1.01–3.51	0.046	1.90	0.99–3.64	0.052	1.60	0.79–3.22	0.191
BMI > = 25 kg/m^2	3.63	1.72–7.65	0.001	3.64	1.77–7.52	<0.001							3.77	1.80–7.93	<0.001
Cardiovascular diseases	1.59	0.61–4.14	0.341	1.78	0.69–4.59	0.231	2.28	1.07–4.89	0.034	1.60	0.71–3.60	0.254	1.60	0.62–4.15	0.334
Cerebrovascular diseases	1.86	0.66–5.24	0.239	1.72	0.62–4.78	0.299	1.84	0.78–4.36	0.166	1.55	0.62–3.90	0.353	1.83	0.65–5.13	0.252
Hypertension	1.09	0.55–2.16	0.804	1.08	0.56–2.10	0.810	1.71	0.94–3.09	0.077	1.48	0.80–2.74	0.215	1.07	0.54–2.11	0.856
Diabetes Mellitus	1.73	0.85–3.53	0.131	1.69	0.84–3.42	0.142							1.66	0.82–3.37	0.161
Respiratory disorders (Chronic lung disease)	1.95	0.87–4.37	0.106	1.80	0.80–4.03	0.154	1.93	0.92–4.06	0.083	2.00	0.94–4.26	0.073	1.86	0.83–4.16	0.130
Albumin, g/dL	0.37	0.17–0.78	0.009	0.40	0.19–0.82	0.012				0.54	0.28–1.05	0.069	0.37	0.17–0.78	0.009
AST, IU/L	1.01	1.00–1.02	0.100												
eGFR <= 60 mL/min/1.73m^2	1.86	0.98–3.53	0.059	1.91	1.01–3.61	0.048	2.06	1.15–3.72	0.016	2.16	1.17–3.99	0.014	1.89	0.99–3.58	0.052
C-reactive protein, mg/dL	1.04	0.98–1.09	0.179	1.04	0.99–1.10	0.143	1.07	1.03–1.12	0.002	1.04	0.99–1.10	0.082	1.04	0.99–1.10	0.130
Lymphocyte count <= 10^3/mL	1.61	0.82–3.13	0.166	1.60	0.83–3.11	0.163	1.70	0.93–3.12	0.086	1.91	1.02–3.60	0.044	1.61	0.82–3.14	0.163
Platelet count 10^3/mL	0.94	0.90–0.99	0.018							0.95	0.91–1.00	0.041	0.95	0.90–1.00	0.072
D-dimer > = 1 mg/dL	0.94	0.45–1.96	0.875	0.95	0.47–1.92	0.887	1.26	0.68–2.33	0.457	1.01	0.50–2.00	0.989	0.96	0.46–2.01	0.924
FIB-4				1.15	1.02–1.29	0.022									
NFS							1.17	1.02–1.34	0.028						
BARD										1.84	1.29–2.64	0.001			
APRI													1.35	0.76–2.38	0.308
Fatty liver	1.34	0.63–2.83	0.449	1.41	0.69–2.89	0.344	2.22	1.23–4.01	0.008	2.72	1.44–5.15	0.002	1.44	0.68–3.01	0.339

APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; FIB-4, fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

Table 5 Multivariate logistic regression analysis of oxygen demand

	Model 1			Model 2 (FIB-4)			Model 3 (NSF)			Model 4 (BARD)			Model 5 (APRI)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age > = 65 years	3.03	1.53–5.98	0.001							2.46	1.28–4.73	0.007	3.04	1.54–6.01	0.001
Gender Male	1.28	0.73–2.26	0.390	1.19	0.69–2.05	0.522	1.50	0.90–2.51	0.123	1.59	0.93–2.73	0.092	1.32	0.75–2.33	0.329
BMI > = 25 kg/m^2	2.25	1.17–4.31	0.015	1.93	1.04–3.58	0.037							2.30	1.21–4.39	0.012
Cardiovascular diseases	0.99	0.38–2.61	0.982	1.08	0.41–2.85	0.872	1.40	0.64–3.06	0.400	0.89	0.39–2.06	0.793	0.99	0.38–2.61	0.99
Hypertension	1.23	0.68–2.23	0.497	1.45	0.81–2.58	0.207	1.77	1.03–3.04	0.040	1.46	0.84–2.53	0.177	1.23	0.68–2.23	0.497
Diabetes Mellitus	1.78	0.91–3.47	0.091	1.74	0.90–3.36	0.098							1.69	0.87–3.29	0.119
Respiratory disorders (Chronic lung disease)	1.50	0.70–3.22	0.298	1.51	0.71–3.21	0.279	1.65	0.81–3.36	0.165	1.73	0.83–3.59	0.142	1.46	0.68–3.12	0.334
Malignancy (Cancer)	1.14	0.40–3.28	0.803	1.24	0.45–3.44	0.678	1.18	0.45–3.08	0.731	1.22	0.46–3.24	0.695	1.11	0.39–3.17	0.848
Albumin, g/dL	0.65	0.35–1.19	0.163	0.57	0.31–1.02	0.057				0.71	0.41–1.25	0.235	0.64	0.35–1.18	0.149
AST, IU/L	1.01	1.00–1.02	0.147												
eGFR <= 60 mL/min/1.73m^2	1.58	0.89–2.80	0.120	1.82	1.03–3.19	0.038	1.85	1.08–3.16	0.024	1.68	0.97–2.93	0.065	1.60	0.90–2.83	0.107
C-reactive protein, mg/dL	1.11	1.04–1.19	0.002	1.11	1.04–1.18	0.001	1.13	1.07–1.20	<0.001	1.11	1.04–1.18	0.001	1.12	1.05–1.19	0.001
Lymphocyte count <= 10^3/mL	1.42	0.83–2.43	0.206	1.36	0.80–2.31	0.254	1.47	0.89–2.41	0.130	1.56	0.93–2.60	0.092	1.42	0.83–2.43	0.202
Platelet count 10^3/mL	0.97	0.93–1.00	0.061							0.97	0.94–1.01	0.121	0.97	0.93–1.01	0.111
D-dimer > = 1 mg/dL	0.95	0.50–1.81	0.870	1.10	0.59–2.03	0.765	1.47	0.84–2.56	0.178	1.00	0.54–1.88	0.994	0.96	0.50–1.83	0.899
FIB-4				1.17	1.01–1.36	0.037									
NFS							1.20	1.00–1.44	0.049						
BARD										1.68	1.23–2.28	0.001			
APRI													1.17	0.64–2.14	0.607
Fatty Liver	1.60	0.83–3.11	0.162	1.64	0.88–3.06	0.119	2.06	1.21–3.50	0.007	2.91	1.64–5.18	<0.001	1.75	0.91–3.37	0.092

AST, aspartate aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; HSI, hepatic steatosis index; NFS, non-alcoholic fatty liver disease fibrosis score.

FIB-4, BARD, and APRI were significant ($P < 0.05$) for all outcomes (Table 2).

Next, we performed the multivariate logistic regression analysis using the values, which was significant on single logistic regression analysis. We excluded the variables that were incorporated to calculate the liver fibrosis scores.

In the multivariate logistic regression analysis using death as objective variable, and explanatory variables other than liver fibrosis scores, age ≥ 65 years, GFR ≤60 mL/min/1.73 m^2, and platelet count were significant (Table 3, Model 1).

When using the FIB-4 as a liver fibrosis score, eGFR ≤60 mL/min/1.73 m^2 and increased FIB-4 were risk factors for death (Table 3, Model 2). We did not use age, AST, and platelet count as variables, because these variables were already incorporated in the FIB-4. Using the NFS as a liver fibrosis score, cardiovascular diseases, eGFR ≤60 mL/min/1.73 m^2, D-dimer ≥1 mg/dL, and increased NFS were risk factors for death (Table 3, Model 3). We did not use age, DM, albumin, AST, and platelet count as variables, because these variables were already incorporated in the NFS score. When using the BARD and APRI as variables for liver fibrosis score, neither increased BARD nor increased APRI were risk factors for death (Table 3, Models 4 and 5).

Risk factors for severe COVID-19. In the multivariate logistic regression analysis using severe COVID-19 as objective variable, and explanatory variables as variables other than liver fibrosis scores, BMI ≥25 kg/m^2, albumin, and platelet count were significant (Table 4, Model 1).

When using the FIB-4 as a liver fibrosis score, BMI ≥25 kg/m^2, decreased albumin, eGFR ≤60 mL/min/1.73 m^2, and increased FIB-4 were risk factors for severe COVID-19 (Table 4, Model 2). Using NFS as the variable for liver fibrosis score, male sex, cardiovascular disease, eGFR ≤60 mL/min/1.73 m^2, increased C-reactive protein, increased NFS, and fatty liver were risk factors for severe COVID-19 (Table 4, Model 3). Using increased BARD as the variable for liver fibrosis score, eGFR ≤60 mL/min/1.73 m^2, BARD, and fatty liver were risk factors for severe COVID-19 (Table 4, Model 4). Using APRI as the variable for liver fibrosis score, BMI ≥25 kg/m^2, and decreased albumin were risk factors for severe COVID-19, whereas increased APRI was not a risk factor (Table 4, Model 5).

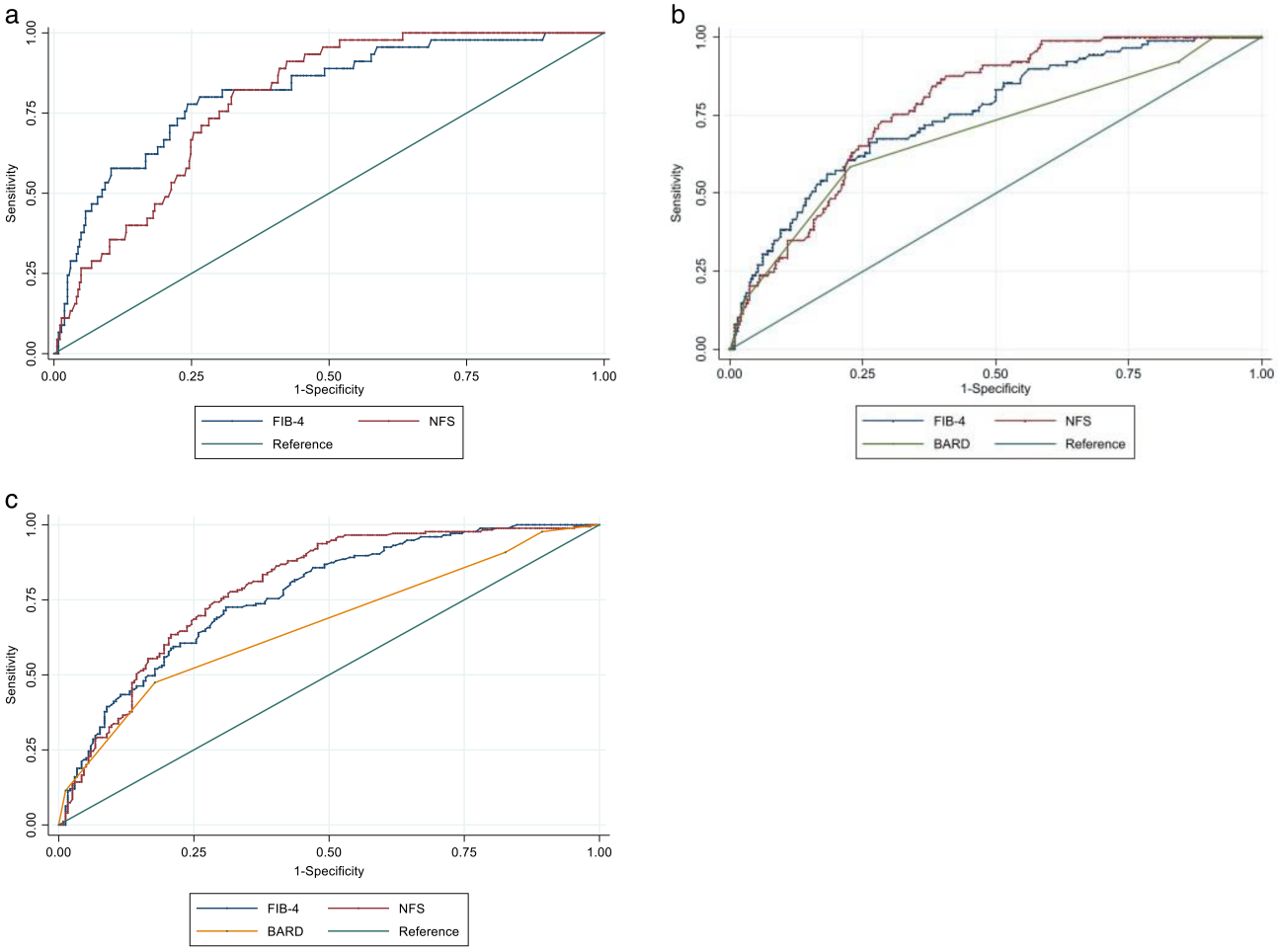

Figure 1 Receiver operating characteristic (ROC) curves for the liver fibrosis scores for death (a), severe COVID-19 (b), and oxygen demand (c). FIB-4, fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

Risk factors for oxygen demand. In the multivariate logistic regression analysis using oxygen demand as objective variable, and explanatory variable as variable other than liver fibrosis scores, age ≥ 65 years, BMI ≥25 kg/m^2, and increased C-reactive protein were significant (Table 5, Model 1).

When using the FIB-4 as a liver fibrosis score, BMI ≥25 kg/m^2, eGFR ≤60 mL/min/1.73 m^2, increased C-reactive protein, and increased FIB-4 were risk factors for oxygen demand (Table 5, Model 2). Using NFS as the variable for liver fibrosis score, hypertension, eGFR ≤60 mL/min/1.73 m^2, increased C-reactive protein, NFS, and fatty liver were risk factors for oxygen demand (Table 5, Model 3). Using BARD as the variable for liver fibrosis score, age ≥ 65 years, eGFR ≤60 mL/min/1.73 m^2, increased BARD, and fatty liver were risk factors for oxygen demand (Table 5, Model 4). Using APRI as variables for liver fibrosis score increased APRI, which was not a risk factor for oxygen demand (Table 5, Model 5).

Predictive ability of fibrotic scores. When fibrotic scores were independent risk factors, we further analyzed the predictive ability of FIB-4, NFS, and BARD using ROC analyses.

The predictive value of FIB-4 for death (area under the curve [AUC] 0.8181, 95%CI 0.7526–0.8837) did not differ from that of NFS (AUC 0.7920, 95%CI 0.7377–0.8464; $P = 0.3712$) (Fig. 1a).

The predictive value of FIB-4 for severe COVID-19 (AUC 0.7545, 95%CI 0.6995–0.8095) did not differ from that of NFS (AUC 0.7815, 95%CI 0.7349–0.8280; $P = 0.2905$) or BARD (AUC 0.6939, 95%CI 0.6336–0.7542; $P = 0.1204$) (Fig. 1b). The predictive value of NFS was significantly higher than that of BARD ($P = 0.0045$).

The predictive value of FIB-4 for oxygen demand (AUC 0.7676, 95%CI 0.7226–0.8126) did not differ from that of NFS (AUC 0.7931, 95%CI 0.7499–0.8362; $P = 0.2275$), but was higher than that of BARD (AUC 0.6663, 95%CI 0.6180–0.7145; $P = 0.001$) (Fig. 1c). The predictive value of NFS was significantly higher than that of BARD ($P < 0.0001$).

Thresholds of fibrotic scores and interaction between fibrotic scores and fatty liver. Youden indexes of FIB-4 and NFS for death were 2.62 and 2.13, respectively. Those of FIB-4, NFS, and BARD for severe COVID-19 were 2.5, 1.56, 2, respectively. Youden indexes of FIB-4, NFS, and BARD for oxygen demand were 1.83, 1.07, and 2, respectively.

Interactions were not observed between fibrotic scores and fatty liver for severe COVID-19 (FIB-4, p for interaction = 0.671; NFS, p for interaction = 0.932; BARD, p for interaction = 0.637). In addition, no interactions were evident for oxygen demand (FIB-4, P for interaction = 0.779; NFS, P for interaction = 0.871; BARD, P for interaction = 0.089).

Finally, we divided patients into two groups using cutoff values of 2.62 for FIB-4, 1.56 for NFS, and 1.07 for NFS, applying the Youden indexes with the highest AUCs among liver fibrosis score associations with death, severe COVID-19, and oxygen demand, respectively, and compared the severity of COVID-19. When using the cutoff value of 2.62 for FIB-4 about death, sensitivity, specificity, positive predictive value, and negative predictive value were 0.80 (95%CI 0.65–0.90), 0.73 (95%CI 0.68–0.78), 0.27 (95%CI 0.19–0.35), and 0.97 (95%CI 0.94–0.99), respectively, and when using the cutoff value of 1.56 for NFS about severe COVID-19, sensitivity, specificity, positive predictive value, and negative predictive value were 0.88 (95% CI 0.79–0.94), 0.44 (95%CI 0.38–0.51), 0.37 (95%CI 0.30–0.44), and 0.91 (95%CI 0.84–0.95) respectively (Table 6). When using the cutoff value of 1.07 for NFS about oxygen demand, sensitivity, specificity, positive predictive value, and negative predictive value were 0.89 (95%CI 0.83–0.93), 0.39 (95%CI 0.32–0.47), 0.61 (95%CI 0.55–0.67), and 0.77 (95%CI 0.65–0.85) respectively.

Discussion

Our study showed that increased FIB-4 and NFS were risk factors for death, and AUCs for these liver fibrosis scores were not different. Increased FIB-4, NFS, and BARD were risk factors for severe COVID-19, and the AUC for FIB-4 did not differ from those for NFS nor BARD, and the AUC for NFS was significantly higher than that of BARD. Increased FIB-4, NFS, and BARD were also risk factors for oxygen demand, and the AUC for FIB-4 did not differ from that for NFS, but was higher than that for BARD, and the AUC for NFS was significantly higher than that of BARD. Furthermore, increased NFS or BARD and fatty liver were independent risk factors for severe COVID-19 and oxygen demand.

Liver injury is known to be very common in cases with severe COVID-19.[37] Elevations of liver fibrosis scores may be multifactorial, but appear related to the pathogenesis and severity of COVID-19. Increasing evidence suggests that both cytokine storm and oxidative stress play essential roles in the progression of COVID-19.[38] Advanced liver disease continues to stimulate

Table 6 Sensitivity, specificity, positive predictive value, and negative predictive value

	Death		Sever COVID-19		Oxygen demand	
	FIB-4 2.62		NFS 1.56		NFS 1.07	
Sensitivity	0.80	0.65–0.90	0.88	0.79–0.94	0.89	0.83–0.93
Specificity	0.73	0.68–0.78	0.44	0.38–0.51	0.39	0.32–0.47
Positive predictive value	0.27	0.19–0.35	0.37	0.30–0.44	0.61	0.55–0.67
Negative predictive value	0.97	0.94–0.99	0.91	0.84–0.95	0.77	0.65–0.85

COVID-19, coronavirus disease 2019.
FIB-4, fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

immune cells and activated immune cells upregulate the production of cytokines, which in turn aggravate systemic inflammatory responses.[39] Furthermore, oxidation of angiotensin-converting enzyme 2 (ACE-2) by reactive oxygen species can increase the affinity of SARS-CoV-2 proteins for ACE-2 and subsequent severity of disease.[40] Thus, the high liver fibrosis factors in this situation may be a reflection of COVID-19 rather than liver fibrosis.

FIB-4 is calculated using age, AST, ALT, and platelet count; NFS is calculated using age, BMI, DM, albumin, AST, ALT, and platelet count; APRI is calculated using AST and ALT; BARD is calculated using BMI, DM, AST, and ALT; and HSI is calculated using sex, BMI, DM, AST, and ALT. Variables of age, sex, BMI, DM, AST, and platelet count are known to represent risk factors for the severity of COVID-19.[41–43] In this study, age, DM, AST, and platelet count correlated with death, severe COVID-19, and oxygen demand in the simple logistic regression analyses. This might reflect the fact that elevated liver fibrosis scores correlated with not only liver fibrosis, but also variables influenced by COVID-19 itself.

Furthermore, in this report, FIB-4 and NFS were the liver fibrosis scores that predicted worse prognosis for COVID-19 more strongly than BARD. Common variables for FIB-4 and NFS are age, AST, ALT, and platelet count, but age and platelet count are not used in APRI, BARD, or HSI. This suggests that advanced age and decreased platelet count might contribute critically to the severity of COVID-19.

As a side note, with regard to fatty liver on CT, Mahamid et al. reported that NAFLD detected by CT represents a high risk for severe COVID-19 irrespective of sex and independent of metabolic syndrome in male patients.[44] In this report, increased NFS or BARD scores and fatty liver evident on CT were independent risk factors for severe COVID-19 and oxygen demand, and fatty liver on CT had no interaction with any liver fibrosis scores, which might represent why elevated liver fibrosis scores were unrelated to liver steatosis but were linked to liver damage from COVID-19.

This study has several limitations. First, the sample size of our cohort was relatively small due to the setting in a single hospital. Second, some confounding factors might have gone unmeasured, such as time-dependent variables, due to the retrospective nature of the study. Third, we diagnosed fatty liver not by liver biopsy but by CT. Therefore, slight fatty liver may not be able to be diagnosed as fatty liver. Fourth, our study did not directly confirm the impact of liver fibrosis scores or fatty liver identified from CT on COVID-19 pathophysiology. Finally, the retrospective nature of the study meant that we were also unable to access information on alcohol intake or markers of hepatitis B and C.

When diagnosing the COVID-19, we may use these results to predict the prognosis and to decide the patients to require intense treatment by calculating the liver fibrosis scores and/or taking the CT. We will construct novel scoring system, which will have better sensitivity and specificity than FIB-4 or NFS, using the significant variables obtained in this study in the future.

In conclusion, our study showed that FIB-4 and NFS were the best liver fibrosis scores that predicted worse prognosis for COVID-19, and that increased NFS or BARD scores and fatty liver evident on CT represent independent risk factors for severe COVID-19 and oxygen demand.

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