

Supplementary material

Liver fibrosis biomarkers accurately exclude advanced fibrosis and are associated with higher cardiovascular risk scores in patients with NAFLD or viral chronic liver disease.

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A. Supplementary Tables.

Table S1. Characteristics of patients with absent-mild vs. significant liver fibrosis in the whole population.

Characteristics	Absent-mild fibrosis (n=180)	Significant fibrosis (n=100)	P
<i>Biometrics</i>			
Age (years)	46.2±11.4	50.3±11.4	0.004
M/F ratio (n, %)	111/69 (62/38)	74/26 (74/26)	0.048
BMI (kg/m ²)	27.0±4.5	28.2±4.4	0.041
WC (cm)	95.1±11.7	100.0±12.6	0.009
Hypertension (n, %)	47 (26)	35 (35)	0.131
Type 2 diabetes (n, %)	21 (12)	25 (25)	0.007
MetS (n, %)	43 (24)	34 (34)	0.093
<i>CVR scores</i>			
SCORE	0.3 (0.1÷1.2)	0.9 (0.2÷1.8)	<0.001
FRS	6.4 (3.2÷12.5)	10.1 (4.9÷18.0)	<0.001
Progetto CUORE	1.7 (0.7÷4.1)	2.8 (1.1÷6.3)	0.003
<i>Laboratory</i>			
Platelet count (x10 ³ /mm ³)	224.2±56.2	191.8±64.9	<0.001
Fasting glucose (mg/dL)	93.0 (85.0÷100.0)	97.5 (92.3÷115.8)	<0.001
Fasting insulin (mIU/L)	10.0 (7.1÷14.8)	12.2 (8.1÷17.0)	0.086
HOMA-IR score	2.4 (1.5÷3.7)	3.1 (2.0÷4.8)	0.017
AST (U/L)	34.8 (26.4÷51.0)	50.0 (36.3÷70.5)	<0.001
ALT (U/L)	56.0 (37.3÷90.8)	91.0 (55.0÷134.2)	<0.001
GGT (U/L)	38.8 (22.0÷60.8)	55.0 (36.0÷104.0)	<0.001
Albumin (g/dL)	4.4±0.4	4.3±0.5	0.024
γ-globulin (mg/dL)	1.2±0.3	1.3±0.5	0.180
TC (mg/dL)	189.6±43.0	181.5±47.7	0.150
HDL-C (mg/dL)	47.2±13.6	45.2±14.4	0.329
LDL-C (mg/dL)	122.4±38.7	113.4±40.3	0.116
TG (mg/dL)	93.0 (71.3÷135.8)	113.0 (68.0÷168.0)	0.158
SUA (mg/dL)	5.2±1.4	5.4±1.5	0.361
Ferritin (mg/dL)	121.5 (62.8÷232.0)	193.0 (111.0÷297.0)	0.001
<i>Liver fibrosis biomarkers</i>			
AAR	0.63 (0.51÷0.74)	0.55 (0.46÷0.72)	0.088
APRI	0.50 (0.31÷0.73)	0.71 (0.47÷1.39)	<0.001
FIB-4	0.93 (0.69÷1.44)	1.37 (0.84÷2.57)	<0.001
Forns	4.4±1.4	5.7±2.1	<0.001

Data are expressed as means (±SD) for continuous variables normally distributed or as medians (25th–75th percentile) for those not normally distributed, and as frequencies (percentages) for categorical variables.

Abbreviations: AAR, AST to ALT ratio; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BMI, body mass index; CVR, cardiovascular risk; F, female; FIB-4, fibrosis-4; FRS, Framingham risk score; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S2. Characteristics of patients with absent-mild vs. significant liver fibrosis according to CLD aetiology.

Characteristics	Viral CLD			NAFLD		
	Absent-mild fibrosis (n=118)	Significant Fibrosis (n=55)	P	Absent-mild fibrosis (n=62)	Significant Fibrosis (n=45)	P
Biometrics						
Age (years)	45.7±11.1	51.8±10.7	<0.001	47.0±11.9	48.47±12.1	0.533
M/F ratio (n, %)	70/48 (59/41)	38/17 (69/31)	0.241	41/21 (66/34)	36/9 (80/20)	0.132
BMI (kg/m ²)	25.9±4.2	26.2±3.1	0.646	28.9±4.4	30.4±4.5	0.077
WC (cm)	90.0±10.4	92.7±9.0	0.260	99.5±11.1	104.7±12.4	0.028
Hypertension (n, %)	27 (23)	17 (31)	0.261	20 (32)	18 (40)	0.422
Type 2 diabetes (n, %)	6 (5)	7 (13)	0.118	15 (24)	18 (40)	0.093
MetS (n, %)	15 (13)	6 (11)	0.808	28 (45)	28 (62)	0.116
CVR scores						
SCORE	0.3 (0.1÷1.1)	0.8 (0.3÷1.6)	0.003	0.5 (0.2÷1.2)	1 (0.2÷2.2)	0.180
FRS	6.2 (3.0÷12.5)	9.2 (4.8÷16.0)	0.013	6.9 (3.5÷13.3)	11.4 (5.4÷26.7)	0.024
Progetto CUORE	1.3 (0.5÷4.0)	1.9 (0.9÷4.2)	0.119	2 (0.9÷4.2)	4.3 (1.8÷8.8)	0.018
Laboratory						
Platelets (x10 ³ /mm ³)	220.0±56.9	176.4±60.5	<0.001	232.0±54.7	210.6±65.7	0.069
Glucose (mg/dL)	92.0 (84.0÷99.0)	97.0 (89.0÷104.0)	0.009	96.0 (88.0÷105.5)	101.0 (94.0÷123.0)	0.045
Insulin (mIU/L)	9.6 (7.1÷15.5)	9.4 (6.7÷16.0)	0.922	10.3 (6.8÷13.1)	14.0 (8.5÷17.9)	0.024
HOMA-IR score	2.4 (1.5÷3.6)	2.5 (1.5÷4.4)	0.367	2.5 (1.5÷3.7)	3.4 (2.2÷5.6)	0.016
AST (U/L)	39.2 (29.0÷57.5)	61.0 (38.0÷88.0)	<0.001	28.0 (24.0÷40.0)	42.0 (29.0÷54.5)	<0.001
ALT (U/L)	60.5 (39.8÷105.5)	107.1 (55.5÷154.8)	0.001	47.0 (35.0÷71.5)	75.0 (53.5÷109.5)	0.001
GGT (U/L)	36.0 (20.0÷48.7)	55.0 (37.0÷89.0)	<0.001	48.5 (30.3÷100.5)	54.0 (35.0÷112.5)	0.333
Albumin (g/dL)	4.4±0.4	4.2±0.5	0.005	4.5±0.5	4.4±0.4	0.545
γ-globulin (mg/dL)	1.31±0.33	1.50±0.45	0.003	1.07±0.21	1.06±0.31	0.987
TC (mg/dL)	175.8±37.0	163.1±37.8	0.038	215.7±41.6	204.0±49.2	0.187
HDL-C (mg/dL)	46.9±13.8	50.8±14.7	0.177	47.5±13.5	40.6±12.5	0.010
LDL-C (mg/dL)	105.3±30.3	96.9±36.0	0.226	141.8±38.3	126.8±39.1	0.058
TG (mg/dL)	83.0 (62.0÷112.0)	81.0 (61.0÷113.0)	0.773	132.0 (89.0÷206.0)	165.0 (117.5÷238.5)	0.103
SUA (mg/dL)	4.8±1.2	4.8±1.2	0.978	6.0±1.5	6.1±1.5	0.850
Ferritin (mg/dL)	111.5 (57.0÷227.8)	176.0 (84.0÷265.0)	0.021	144.5 (83.8÷241.0)	210.5 (121.0÷359.0)	0.015
Liver fibrosis biomarkers						
AAR	0.65 (0.53÷0.75)	0.64 (0.50÷0.73)	0.625	0.59 (0.48÷0.69)	0.49 (0.42÷0.68)	0.054
APRI	0.55 (0.35÷0.85)	1.11 (0.60÷1.68)	<0.001	0.38 (0.27÷0.54)	0.61 (0.38÷0.81)	0.001
Fib4	1.04 (0.74÷1.56)	1.93 (1.05÷3.05)	<0.001	0.76 (0.63÷1.09)	1.03 (0.64÷1.73)	0.059
Forns	4.5±1.4	6.3±1.9	<0.001	4.2±1.4	5.0±2.1	0.026
NFS				-2.05±1.29	-1.35±2.01	0.045
BARD				1 (0÷2)	1 (0÷2)	0.208
HFS				0.04 (0.01÷0.07)	0.06 (0.02÷0.20)	0.026

Data are expressed as means (±SD) for continuous variables normally distributed or as medians (25th–75th percentile) for those not normally distributed, and as frequencies (percentages) for categorical variables.

Abbreviations: AAR, AST to ALT ratio; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BARD, BMI AAR Diabetes; BMI, body mass index; CVR, cardiovascular risk; F, female; FIB-4, fibrosis-4; FRS, Framingham risk score; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; HFS, Hepamet fibrosis score; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; NFS, NAFLD fibrosis score; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S3. Characteristics of patients with absent-to-moderate vs. advanced liver fibrosis in the whole population.

Characteristics	Absent to moderate fibrosis (n=242)	Advanced Fibrosis (n=38)	P
<i>Biometrics</i>			
Age (years)	46.3±11.5	56.0±8.0	<0.001
M/F ratio (n, %)	159/83 (66/34)	26/12 (68/32)	0.854
BMI (kg/m ²)	27.3±4.4	28.7±5.0	0.069
WC (cm)	96.4±11.3	101.4±16.9	0.158
Hypertension (n, %)	63 (26)	19 (50)	0.004
Diabetes (n, %)	30 (12)	16 (42)	<0.001
MetS (n, %)	63 (26)	14 (38)	0.175
<i>CVR scores</i>			
SCORE	0.4 (0.1÷1.3)	1.3 (0.8÷3.0)	<0.001
FRS	6.7 (3.2÷12.9)	15.7 (8.9÷27.8)	<0.001
Progetto CUORE	1.8 (0.8÷4.2)	5.7 (2.5÷12.2)	<0.001
<i>Laboratory</i>			
Platelets (x10 ³ /mm ³)	221.9±55.8	153.2±62.6	<0.001
Glucose (mg/dL)	94.0 (86.0÷101.0)	99.0 (92.5÷139.5)	0.002
Insulin (mIU/L)	10.6 (7.1÷15.7)	10.7 (7.8÷19.4)	0.516
HOMA-IR score	2.5 (1.6÷3.8)	3.2 (2.0÷6.9)	0.075
AST (U/L)	37.0 (27.7÷53.3)	62.8 (46.5÷82.1)	<0.001
ALT (U/L)	61.0 (40.8÷107.3)	93.0 (55.9÷143.3)	0.004
GGT (U/L)	40.0 (25.5÷66.5)	71.5 (47.8÷141.3)	<0.001
Albumin (g/dL)	4.4±0.4	4.2±0.4	0.001
γ-globulin (mg/dL)	1.2±0.4	1.4±0.5	0.086
TC (mg/dL)	189.8±45.2	166.7±36.6	0.003
HDL-C (mg/dL)	46.4±14.0	46.3±14.1	0.976
LDL-C (mg/dL)	120.9±39.8	103.6±34.8	0.049
TG (mg/dL)	95.0 (69.0÷148.0)	115.0 (75.5÷145.3)	0.402
SUA (mg/dL)	5.3±1.4	5.1±1.4	0.540
Ferritin (mg/dL)	144.5 (75.3÷245.8)	184.0 (92.0÷378.0)	0.070
<i>Liver fibrosis biomarkers</i>			
AAR	0.61 (0.48÷0.72)	0.67 (0.52÷0.85)	0.042
APRI	0.51 (0.32÷0.74)	1.26 (0.76÷1.75)	<0.001
FIB-4	0.96 (0.69÷1.46)	2.53 (1.73÷3.59)	<0.001
Forns	4.5±1.5	7.3±1.6	<0.001

Data are expressed as means (±SD) for continuous variables normally distributed or as medians (25th–75th percentile) for those not normally distributed, and as frequencies (percentages) for categorical variables.

Abbreviations: AAR, AST to ALT ratio; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BMI, body mass index; CVR, cardiovascular risk; F, female; FIB-4, fibrosis-4; FRS, Framingham risk score; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S4. Characteristics of patients with absent-to-moderate vs. advanced liver fibrosis according to CLD etiology.

Characteristics	Viral CLD (n=173)		P	NAFLD (n=107)		P
	Absent-to-moderate fibrosis (n=149)	Advanced fibrosis (n=24)		Absent-to-moderate fibrosis (n=93)	Advanced fibrosis (n=14)	
Biometrics						
Age (years)	46.5±11.4	54.8±7.6	<0.001	46.1±11.6	58.0±8.5	<0.001
Sex M/F (n, %)	93/56 (62/38)	15/9 (63/37)	1.000	66/27 (71/29)	11/3 (79/21)	0.753
WC (cm)	91.2±9.9	89.9±10.5	0.688	100.3±10.7	111.1±15.2	0.021
Hypertension (n, %)	35 (24)	9 (37)	0.205	28 (30)	10 (71)	0.005
BMI (kg/m ²)	25.9±3.9	26.6±3.9	0.452	29.1±4.4	32.0±4.9	0.025
Type 2 diabetes (n, %)	9 (6)	4 (17)	0.086	21 (23)	12 (86)	<0.001
MetS (n, %)	18 (12)	3 (12)	1.000	45 (48)	11 (79)	0.045
CVR scores						
SCORE	0.3 (0.6÷1.2)	1.0 (0.5÷2.8)	0.002	0.4 (0.1÷1.4)	2.2 (1.2÷3.3)	<0.001
FRS	6.4 (3.2÷12.6)	11.4 (5.0÷18.0)	0.009	7.3 (3.4÷15.0)	27.8 (14.7÷45.5)	<0.001
Progetto CUORE	1.5 (0.5÷4.0)	2.6 (1.0÷5.7)	0.152	2.0 (0.9÷4.5)	9.4 (5.1÷17.7)	<0.001
Laboratory						
Platelets (x10 ³ /mm ³)	216.1±56.3	144.8±56.5	<0.001	231.3±53.9	167.6±71.8	<0.001
Glucose (mg/dL)	93.0 (84.0÷100.0)	94.0 (88.0÷112.0)	0.242	96.0 (89.0÷108.5)	132.0 (101.8÷191.8)	<0.001
Insulin (mIU/L)	9.7 (7.1÷15.9)	8.7 (6.8÷14.9)	0.719	11.5 (7.8÷15.4)	13.7 (8.7÷27.1)	0.150
HOMA-IR score	2.4 (1.5÷3.6)	2.3 (1.5÷4.8)	0.632	2.7 (1.7÷4.1)	4.1 (2.1÷12.2)	0.024
AST (U/L)	40.5 (30.5÷60.0)	73.1 (55.0÷93.3)	<0.001	31.0 (25.0÷42.0)	50.2 (45.0÷56.3)	<0.001
ALT (U/L)	64.0 (42.0÷123.5)	124.5 (75.8÷166.5)	0.006	58.0 (39.5÷94.0)	75.0 (44.4÷92.0)	0.224
GGT (U/L)	37.0 (22.5÷54.0)	72.4 (42.3÷136.3)	<0.001	48.0 (31.0÷96.5)	71.5 (47.8÷154.0)	0.023
Albumin (g/dL)	4.4±0.4	4.2±0.4	0.015	4.5±0.43	4.2±0.52	0.030
γ-globulin (mg/dL)	1.34±0.37	1.55±0.44	0.014	1.06±0.24	1.09±0.37	0.816
TC (mg/dL)	173.9±38.9	158.9±25.5	0.019	215.4±42.9	180.1±48.6	0.006
HDL-C (mg/dL)	47.4±14.1	55.8±12.6	0.061	45.3±13.8	38.9±10.5	0.096
LDL-C (mg/dL)	103.0±32.7	96.0±31.8	0.519	139.1±38.2	109.6±37.1	0.010
TG (mg/dL)	81.0 (62.0÷109.5)	93.0 (63.0÷123.0)	0.356	145.0 (89.0÷234.3)	146.0 (119.0÷215.0)	0.815
SUA (mg/dL)	4.8±1.2	4.9±1.4	0.778	6.1±1.5	5.5±1.4	0.182
Ferritin (mg/dL)	122.5 (62.0÷232.0)	184.0 (114.0÷384.0)	0.065	178.0(100.8÷247.8)	193.0 (85.8÷392.5)	0.561
Liver fibrosis biomarkers						
AST/ALT AAR	0.64 (0.51÷0.74)	0.68 (0.55÷0.76)	0.357	0.56 (0.45÷0.67)	0.59 (0.51÷0.99)	0.054
APRI	0.59 (0.39÷0.89)	1.52 (1.17÷1.88)	<0.001	0.41 (0.29÷0.63)	0.85 (0.65÷1.20)	<0.001
Fib4	1.07 (0.77÷1.60)	2.58 (2.13÷3.54)	<0.001	0.74 (0.61÷1.10)	2.19 (1.31÷3.73)	<0.001
Forns	4.7±1.5	7.5±1.6	<0.001	4.1±1.4	7.1±1.8	<0.001
NFS				-2.08±1.40	0.43±1.62	<0.001
BARD				1 (0÷1)	2 (2÷4)	0.001
HFS				0.04 (0.01÷0.07)	0.34 (0.19÷0.70)	<0.001

Data are expressed as means (±SD) for continuous variables normally distributed or as medians (25th–75th percentile) for those not normally distributed, and as frequencies (percentages) for categorical variables.

Abbreviations: AAR, AST to ALT ratio; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BARD, BMI AAR Diabetes; BMI, body mass index; CVR, cardiovascular risk; F, female; FIB-4, fibrosis-4; FRS, Framingham risk score; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; HFS, Hepamet fibrosis score; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; NFS, NAFLD fibrosis score; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S5. Characteristics of patients with simple steatosis vs. NASH in the NAFLD population.

Characteristics	Simple steatosis (n=30)	NASH (n=77)	P
Biometrics			
Age (years)	46.2±12.5	48.2±11.8	0.446
M/F ratio (n, %)	21/9 (70/30)	56/21 (73/27)	0.813
BMI (kg/m ²)	26.9±3.5	30.5±4.5	<0.001
WC (cm)	93.8±8.0	104.7±11.8	<0.001
Hypertension (n, %)	6 (20)	32 (42)	0.044
Type 2 diabetes (n, %)	7 (23)	26 (34)	0.356
MetS (n, %)	8 (27)	48 (62)	0.001
CVR scores			
SCORE	0.6 (0.1÷1.3)	0.7 (0.2÷1.9)	0.433
FRS	6.5 (3.1÷12.1)	10.4 (4.1÷23.7)	0.057
Progetto CUORE	1.8 (0.8÷3.6)	3.5 (1.1÷7.0)	0.016
Laboratory			
Platelet count (x10 ³ /mm ³)	230.0±50.5	220.3±63.7	0.453
Fasting glucose (mg/dL)	95.5 (87.8÷110.5)	98.0 (91.5÷119.0)	0.179
Fasting insulin (mIU/L)	7.3 (5.2÷10.6)	13.0 (9.5÷17.8)	<0.001
HOMA-IR score	1.7 (1.3÷2.4)	3.4 (2.3÷4.7)	<0.001
AST (U/L)	27.9 (20.8÷35.3)	38.0 (27.0÷53.0)	0.002
ALT (U/L)	41.0 (35.0÷63.3)	65.0 (45.0÷106.0)	0.002
GGT (U/L)	48.0 (35.5÷101.3)	51.0 (31.5÷110.0)	0.920
Albumin (g/dL)	4.6±0.4	4.4±0.5	0.206
γ-globulin (mg/dL)	1.1±0.3	1.1±0.3	0.962
TC (mg/dL)	221.0±45.3	206.8±44.6	0.145
HDL-C (mg/dL)	50.7±14.1	42.1±12.5	0.004
LDL-C (mg/dL)	142.8±38.5	132.4±39.2	0.243
TG (mg/dL)	107.0 (78.8÷189.8)	153.0 (115.0÷237.0)	0.035
SUA (mg/dL)	5.4±1.4	6.3±1.4	0.004
Ferritin (mg/dL)	132.0 (86.0÷226.0)	195.0 (102.7÷319.5)	0.062
Liver histology			
Significant fibrosis (n, %)	2 (7)	43 (56)	<0.001
Advanced fibrosis (n, %)	0 (0)	14 (18)	0.010
Cirrhosis (n, %)	0 (0)	5 (6)	0.319
Liver fibrosis biomarkers			
AAR	0.59 (0.51÷0.70)	0.51 (0.43÷0.68)	0.106
APRI	0.36 (0.23÷0.48)	0.51 (0.34÷0.72)	0.005
FIB-4	0.73 (0.58÷1.1)	0.91 (0.66÷1.42)	0.091
Forns	4.1±1.6	4.7±1.8	0.140
NFS	-2.30±1.37	-1.54±1.72	0.033
BARD	1 (0÷1)	1 (1÷2)	0.018
HFS	0.02 (0.01÷0.07)	0.05 (0.02÷0.16)	0.008

Data are expressed as means (±SD) for continuous variables normally distributed or as medians (25th–75th percentile) for those not normally distributed, and as frequencies (percentages) for categorical variables.

Abbreviations: AAR, AST to ALT ratio; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BARD, BMI AAR Diabetes; BMI, body mass index; CVR, cardiovascular risk; F, female; FIB-4, fibrosis-4; FRS, Framingham risk score; GGT, gamma-glutamyl transferase; HDL-C, high density lipoprotein cholesterol; HFS, Hepamet fibrosis score; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; M, male; MetS, metabolic syndrome; NFS, NAFLD fibrosis score; NASH, nonalcoholic steatohepatitis; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table S6. Diagnostic performance of liver fibrosis biomarkers for predicting significant liver fibrosis in the whole population (n=280).

	Cut-offs	SE	SP	PPV	NPV	ACC	LR+	LR-	AUROC (95%CI)
AAR	≥ 0.8	15.0	81.7	31.3	63.4	57.9	0.82	1.04	0.44 (0.40-0.51)
	> 1	9.0	93.9	45.0	65.0	63.6	1.47	0.97	
APRI	> 0.5	72.0	51.7	45.3	76.9	58.9	1.49	0.54	0.68 (0.62- 0.75)
	> 0.7	50.0	70.6	48.5	71.8	63.2	1.70	0.71	
	> 1.5	19.0	94.4	65.5	67.7	67.5	3.42	0.86	
Fib-4	≥ 1.45	48.0	75.0	51.6	72.2	65.4	1.92	0.69	0.66 (0.59-0.73)
	> 3.25	18.0	97.8	81.8	68.2	69.3	8.10	0.84	
Forns	≥ 4.2	78.0	47.2	45.1	79.4	58.2	1.48	0.47	0.69 (0.63-0.76)
	> 6.9	29.0	95.6	78.4	70.8	71.8	6.53	0.74	

Significant fibrosis was defined as histologic liver fibrosis \geq F3 according to Ishak et al. [29] for viral CLD and \geq F2 according to Brunt/Kleiner et al. for NAFLD [27, 28].

Abbreviations: AAR, AST to ALT ratio; ACC, accuracy; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristics; CLD, chronic liver disease; Fib-4, fibrosis 4; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity.

Table S7. Diagnostic performance of liver fibrosis biomarkers for predicting significant fibrosis in patients with viral CLD (n=173).

	Cut-offs	SE	SP	PPV	NPV	ACC	LR+	LR-	AUROC (95%CI)
AAR	≥ 0.8	14.6	79.7	25.0	66.7	59.0	0.72	1.07	0.48 (0.38-0.57)
	> 1	9.1	93.2	38.5	68.8	66.5	1.34	0.98	
APRI	> 0.5	83.6	42.4	40.4	84.8	55.5	1.45	0.39	0.73 (0.65-0.81)
	> 0.7	63.6	61.9	43.8	78.5	62.4	1.67	0.59	
	> 1.5	30.9	92.4	65.4	74.3	72.8	4.05	0.75	
FIB-4	≥1.45	60.0	68.6	47.1	78.6	65.9	1.91	0.58	0.73 (0.65-0.81)
	> 3.25	21.8	97.5	80.0	72.8	73.4	8.58	0.80	
Forns	≥ 4.2	89.1	42.4	41.9	89.3	57.2	1.55	0.26	0.77 (0.69-0.85)
	> 6.9	40.0	95.8	81.5	77.4	78.0	9.44	0.63	

Significant fibrosis was defined as histologic liver fibrosis ≥F3 according to Ishak et al. [29].

Abbreviations: AAR, AST to ALT ratio; ACC, accuracy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, ALT to Platelet Ratio Index; AUROC, area under the receiver operating characteristics; CLD, chronic liver disease; FIB-4, fibrosis 4; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity.

Table S8. Diagnostic performance of liver fibrosis biomarkers for predicting significant fibrosis in patients with NAFLD (n=107).

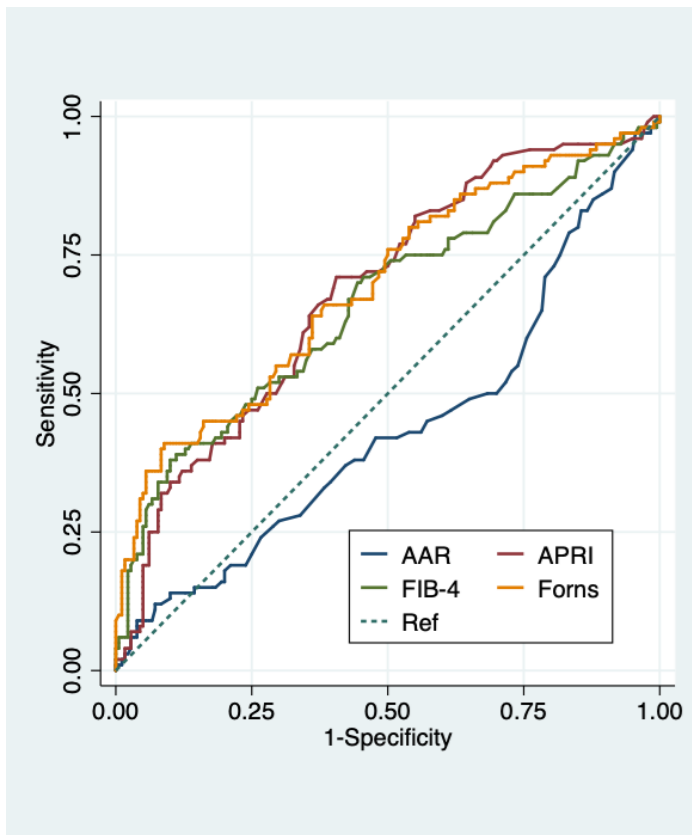
	Cut-offs	SE	SP	PPV	NPV	ACC	LR+	LR-	AUROC (95% CI)
AAR	≥ 0.8	15.6	85.5	43.8	58.2	56.1	1.07	0.99	0.39 (0.28-0.51)
	> 1	8.9	95.2	57.1	59.0	58.9	1.84	0.96	
APRI	> 0.5	57.8	69.4	57.8	69.4	64.5	1.89	0.61	0.69 (0.59-0.80)
	> 0.7	33.3	87.1	65.2	64.3	64.5	2.58	0.77	
	> 1.5	4.4	98.4	66.7	58.7	58.9	2.76	0.97	
FIB-4	≥ 1.3	37.8	85.5	65.4	65.4	65.4	2.60	0.73	0.61 (0.49-0.72)
	> 2.67	13.3	96.8	75.0	60.6	61.7	4.13	0.90	
	≥1.45	33.3	87.1	65.2	64.3	64.5	2.58	0.77	
	> 3.25	13.3	98.4	85.7	61.0	62.6	8.27	0.88	
Forns	≥ 4.2	64.4	56.5	51.8	68.6	59.8	1.48	0.63	0.62 (0.52-0.73)
	> 6.9	15.6	95.2	70.0	60.8	61.7	3.21	0.89	
NFS	≥ -1.455	53.3	66.1	53.3	66.1	60.8	1.58	0.71	0.61 (0.50-0.73)
	> 0.675	15.6	96.8	77.8	61.2	62.6	4.82	0.87	
BARD	≥ 2	37.8	72.6	50.0	61.6	57.9	1.38	0.86	0.56 (0.45-0.67)
HFS	≥ 0.12	31.1	88.7	66.7	64.0	64.5	2.76	0.78	0.63 (0.52-0.74)
	> 0.47	20.0	98.4	90.0	62.9	65.4	12.4	0.81	

Significant fibrosis was defined as histologic liver fibrosis ≥F2 according to Brunt/Kleiner et al. [27, 28].

Abbreviations: AAR, AST to ALT ratio; ACC, accuracy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, ALT to Platelet Ratio Index; AUROC, area under the receiver operating characteristics; BARD, BMI AAR Diabetes; CLD, chronic liver disease; FIB-4, fibrosis-4; HFS, Hepamet fibrosis score; LR, likelihood ratio; NFS, NAFLD fibrosis score; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity.

B. Supplementary Figures.

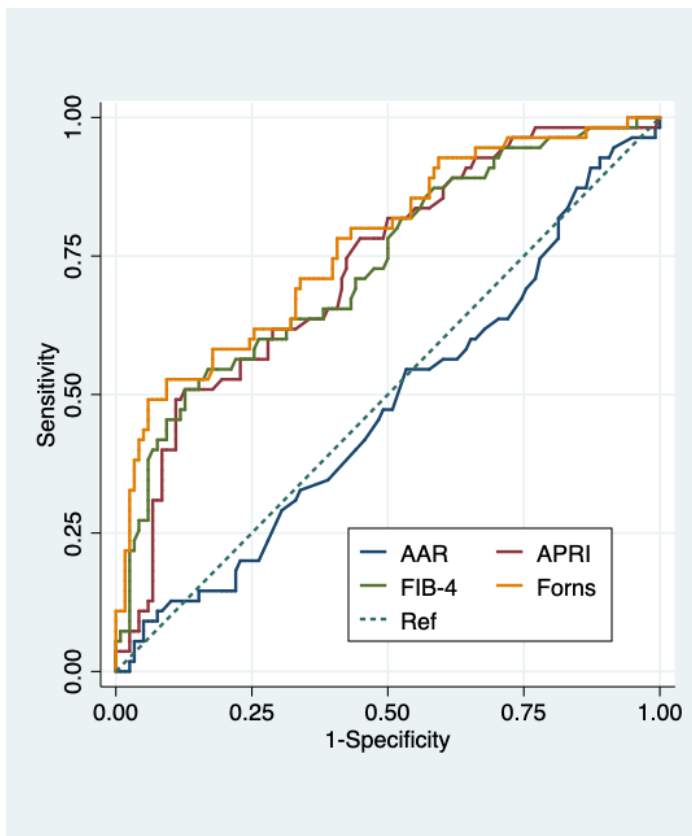
Figure S1. Diagnostic performance of serum biomarkers for predicting significant fibrosis in all patients.



Receiver operating characteristic (ROC) curves of serum biomarkers for the diagnosis of significant fibrosis in all patients. AUROC (95% CI): 0.44 (0.40-0.51) for AAR, 0.68 (0.62- 0.75) for APRI, 0.66 (0.59-0.73) for Fib-4, 0.69 (0.63-0.76) for Forns index. Significant fibrosis was defined as histologic liver fibrosis \geq F3 according to Ishak et al. [29] for viral CLD, and \geq F2 according to Brunt/Kleiner et al. for NAFLD [27, 28].

AAR, AST to ALT ratio; APRI, AST to Platelet Ratio Index; Fib-4, fibrosis 4.

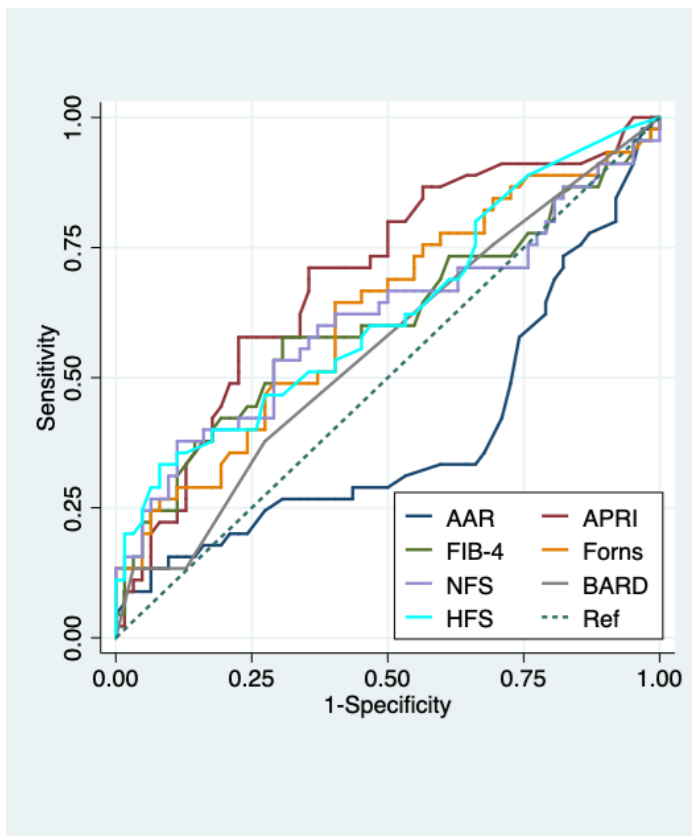
Figure S2. Diagnostic performance of serum biomarkers for predicting significant fibrosis in viral CLD patients.



ROC curves of serum biomarkers for the diagnosis of significant fibrosis in viral CLD patients. AUROC (95% CI): 0.48 (0.38-0.57) for AAR, 0.73 (0.65-0.81) for APRI, 0.73 (0.65-0.81) for FIB-4, 0.77 (0.69-0.85) for Forns index. Significant fibrosis was defined as histologic liver fibrosis \geq F3 according to Ishak et al. [29].

AAR, AST to ALT ratio; APRI, AST to Platelet Ratio Index; Fib-4, fibrosis 4.

Figure S3. Diagnostic performance of serum biomarkers for predicting significant fibrosis in NAFLD patients.



ROC curves of serum biomarkers for the diagnosis of significant fibrosis in NAFLD patients. AUROC (95% CI): 0.39 (0.28-0.51) for AAR, 0.69 (0.59-0.80) for APRI, 0.61 (0.49-0.72) for FIB-4, 0.62 (0.52-0.73) for Forns index, 0.61 (0.50-0.73) for NFS, 0.63 (0.52-0.74) for HFS, 0.56 (0.45-0.67) for BARD. Advanced fibrosis was defined as histologic liver fibrosis \geq F4 according to Ishak et al. [29] for viral CLD, and \geq F3 according to Brunt/Kleiner et al. for NAFLD [27, 28].

AAR, AST to ALT ratio; APRI, AST to Platelet Ratio Index; BARD, BMI AAR Diabetes; Fib-4, fibrosis 4; HFS, Hepamet fibrosis score; NFS, NAFLD fibrosis score.