Table S1. Examples of different APRI cut-offs for the non-invasive identification of significant (≥F2) liver fibrosis in patients with CLD of different etiologies.

CLD etiology	Cut-off(s)	Number of studies (number of patients)	Reference (#PMID)
CHC	0.4	5 (836)	Hepatology. 2011;53:726-736 (21319189)
	<0.5	11 (2052)	
	0.6	3 (531)	
	0.7	4 (609)	
	1	3 (821)	
	0.6-1.0	13 (2424)	
CHB	0.235-0.425	4 (1260)	Hepatology. 2015;61:292-302 (25132233)
	0.535-0.85	5 (906)	
MASLD	0.2	1 (101)	Obes Surg. 2017;27:115-125 (27220852)
	0.4	1 (73)	Obes Surg. 2020;30:1249-1257 (31953745)
	0.43	1 (242)	J Gastroenterol Hepatol. 2011;26:1536-1543 (21950746)
	0.43	1 (373)	Front Endocrinol (Lausanne). 2023;14:1090598 (36793287)
	0.45	1 (100)	BMJ Open Gastroenterol. 2019;6:e000288 (31275584)
	0.6	1 (207)	United European Gastroenterol J. 2019;7:1124-1134 (31662869)
	0.70	1 (251)	Front Med (Lausanne). 2022;9:869190 (35492369)
	0.77	1 (52)	J Gastroenterol. 2008;43:720-728 (18807134)

Table S2. Examples of different FIB-4 cut-offs for the non-invasive identification of significant (≥F2) liver fibrosis in patients with CLD of different etiologies.

CLD etiology	Cut-off(s)	Number of studies (number of patients)	Reference (#PMID)
CHC	1.0	1 (830)	Hepatology. 2006;43:1317-1325. (16729309)
	1.0	1 (100)	Hepatol Res. 2015;45:560-570. (24995544)
	1.17	1 (100)	J Med Virol. 2020. (32558950)
	1.505	1 (208)	Cells. 2019;8:1003. (31470644)
	1.86	1 (107)	Clin Chim Acta. 2008;397:51-54. (18692034)
	1.86	1 (138)	Biomed Res Int. 2019;2019:2639248. (31061822)
	2.2	1 (110)	Hepatol Res. 2016;46:752-757. (26583748)
CHB	0.4	1 (390)	World J Gastroenterol. 2017;23:7425-7432. (29151696)
	0.8-1.1	5 (1026)	Hepatology. 2015;61:292-302. (25132233)
	0.96	1 (179)	Med Mal Infect. 2019;49:607-615. (30871816)
	1.38	1 (126)	J Magn Reson Imaging. 2017;45:1186-1194. (27563840)
	1.59	1 (319)	J Viral Hepat. 2014;21:917-920. (25131445)
MASLD	0.46	1 (373)	Front Endocrinol (Lausanne). 2023;14:1090598. (36793287)
	0.66	1 (73)	Obes Surg. 2020;30:1249-1257. (31953745)
	0.74	1 (101)	Obes Surg. 2017;27:115-125. (27220852)
	0.89	1 (207)	United European Gastroenterol J. 2019;7:1124-1134. (31662869)
	1.45	1 (242)	J Gastroenterol Hepatol. 2011;26:1536-1543. (21950746)
	1.73	1 (251)	Front Med (Lausanne). 2022;9:869190. (35492369)

Table S3. Comparison of DOC, APRI and FIB-4 between F0-1 and F2-4 in all CLD patients.

NIT	F0-1 (n=358)	F2-4 (n=194)	*P* value	Odds ratio (95% CI)	*P* value
DOC, U/µL	1.95 (1.74, 2.19)	2.48 (2.17, 3.07)	<0.0001	8.32 (4.96-13.94)	<0.0001
APRI	0.39 (0.28, 0.60)	0.89 (0.50, 1.60)	<0.0001	0.80 (0.66-0.97)	0.023
FIB-4	1.23 (0.73, 1.90)	2.13 (1.12, 3.40)	<0.0001	1.41 (1.09-1.82)	0.009

Note: Data are presented as medians (inter-quartiles). *P* values based on the Mann-Whitney U test for quantitative data with non-normal distribution. Multivariable logistic regression models (Odds ratios and corresponding 95%CIs) were adjusted for sex and age (reference group F0-1).

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index; NIT, non-invasive test.

Table S4. Clinical characteristics of pooled CLD cohorts stratified by age.

	≤35 years (n=198)	36-45 years (n=150)	46-55 years (n=127)	56-64 years (n=48)	≥65 years (n=29)	*P*-value
Male sex, n (%)	147 (74.2)	106 (70.7)	66 (52.0)	29 (60.4)	7 (24.1)	<0.001
Age, years	30.0 (25.5, 30.0)	40.0 (38.0, 43.0)	50.0 (47.0, 53.0)	59.0 (57.0, 62.0)	67.0 (66.0, 70.0)	<0.001
SF, n (%)	49 (24.7)	45 (30)	61 (48.0)	21 (43.7)	18 (62.1)	<0.001
DOC, U/μL	2.01 (1.78, 2.30)	2.00 (1.80, 2.43)	2.18 (1.82, 2.66)	2.25 (1.96, 2.74)	2.56 (2.19, 3.02)	<0.001
APRI	0.44 (0.28, 0.70)	0.47 (0.32, 0.87)	0.55 (0.35, 1.17)	0.51 (0.30, 0.99)	0.85 (0.39, 1.41)	<0.01
FIB-4	0.87 (0.61, 1.72)	1.44 (0.83, 2.04)	1.78 (1.28, 2.59)	1.95 (1.54, 2.74)	2.56 (2.19, 3.02)	<0.001

Note: Data for age, DOC, APRI and FIB-4 are presented as medians (inter-quartiles). The clinical and biochemistry parameters across the five age groups were compared using the Kruskal-Wallis test for continuous variables and $\chi 2$ test for categorical variables.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index; SF, significant fibrosis (histologically defined by ≥F2 liver fibrosis).

Table S5. Comparison of clinical characteristics between healthy controls (HC) and all CLD patients.

	HC (n=275)	CLD (n=552)	*P* value	Odds ratio (95% CI)	*P* value
Male sex, n (%)	185 (67.3)	355 (64.3)	0.399	\	\
Age, years	41.0 (30.0, 53.0)	40.0 (32.0, 50.0)	0.871	\	\
DOC, U/μL	1.77 (1.62, 1.91)	2.10 (1.80, 2.40)	<0.0001	16.66 (4.93-56.34)	<0.0001
ALT, U/L	19.0 (14.0, 26.0)	49.0(30.0, 94.2)	<0.0001	1.10 (1.06-1.14)	<0.0001
AST, U/L	19.0 (16.0, 23.0)	37.0 (26.0, 63.2)	<0.0001	1.07 (1.01-1.13)	0.022
TB, μmol/L	13.0 (10.0, 17.0)	13.0 (9.9, 18.0)	0.741	1.11 (1.05-1.16)	<0.0001
DB, μmol/L	4.10 (2.60, 5.60)	4.00 (3.00, 6.00)	0.282	0.83 (0.76-0.92)	<0.0001
ALB, g/L	46.3 (42.9, 48.8)	37.8 (9.0, 43.5)	<0.0001	0.74 (0.69-0.80)	<0.0001

Note: Data are presented as proportions, medians (inter-quartiles) according to the original data distribution. *P* values based on the Mann-Whitney U test for quantitative data with non-normal distribution, and the chi-square test for qualitative data. Multivariable logistic regression models (Odds ratios and corresponding 95%CIs) were adjusted for sex and age (reference group HC).

Abbreviations: DOC, dithiothreitol-oxidizing capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; DB, direct bilirubin; ALB, albumin.

Table S6. Comparison of clinical characteristics between healthy controls (HC) and patients with significant (≥F2) liver fibrosis.

	HC (n=275)	F2-4 (n=194)	*P* value	Odds ratio (95% CI)	*P* value
Male sex, n (%)	185 (67.3)	109 (56.2)	0.014	\	\
Age, years	41.0 (30.0, 53.0)	46.0 (35.0, 54.0)	0.008	\	\
DOC, U/μL	1.77 (1.62, 1.91)	2.48 (2.17, 3.07)	<0.0001	10751 (216-534538)	<0.0001
ALT, U/L	19.0 (14.0, 26.0)	72.0 (39.0, 139.5)	<0.0001	1.06 (0.99-1.15)	0.084
AST, U/L	19.0 (16.0, 23.0)	55.0 (35.0, 94.0)	<0.0001	1.15 (1.00-1.31)	0.046
TB, μmol/L	13.0 (10.0, 17.0)	15.2 (12.0, 23.7)	<0.0001	1.22 (1.05-1.42)	0.008
DB, μmol/L	4.10 (2.60, 5.60)	5.00 (3.00, 9.00)	<0.0001	0.71 (0.56-0.89)	0.003
ALB, g/L	46.3 (42.9, 48.8)	35.4 (10.0, 41.0)	<0.0001	0.65 (0.52-0.82)	<0.0001

Note: Data are presented as proportions, medians (inter-quartiles) according to the original data distribution. *P* values based on the Mann-Whitney U test for quantitative data with non-normal distribution, and the chi-square test for qualitative data. Multivariable logistic regression models (Odds ratios and corresponding 95%CIs) were adjusted for sex and age (reference group HC).

Abbreviations: DOC, dithiothreitol-oxidizing capacity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; DB, direct bilirubin; ALB, albumin.

Table S7. Comparison between DOC and LiverRisk, APRI or FIB-4 diagnostic performance for staging significant (≥F2) liver fibrosis in CLD patients.

NIT	Cut-off	AUROC	*P*-value vs. DOC	Sens (%)	Spec (%)	PPV (%)	NPV (%)
DOC, U/μL	2.13	0.790 (0.742-0.833)	\	76.9	71.4	51.1	88.8
LiverRisk, kPa	6.50	0.666 (0.612-0.718)	< 0.001	67.0	64.1	42.1	83.3
APRI	0.59	0.700 (0.647-0.749)	< 0.01	64.8	73.5	48.8	84.3
FIB-4	1.74	0.647 (0.593-0.699)	< 0.001	39.6	85.5	51.4	78.4

Note: A total of 325 CLD patients (203 from CHB (WZ) *plus* 122 from MASLD) with LiverRisk scores available were used for the analyses.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index; NIT, non-invasive test; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

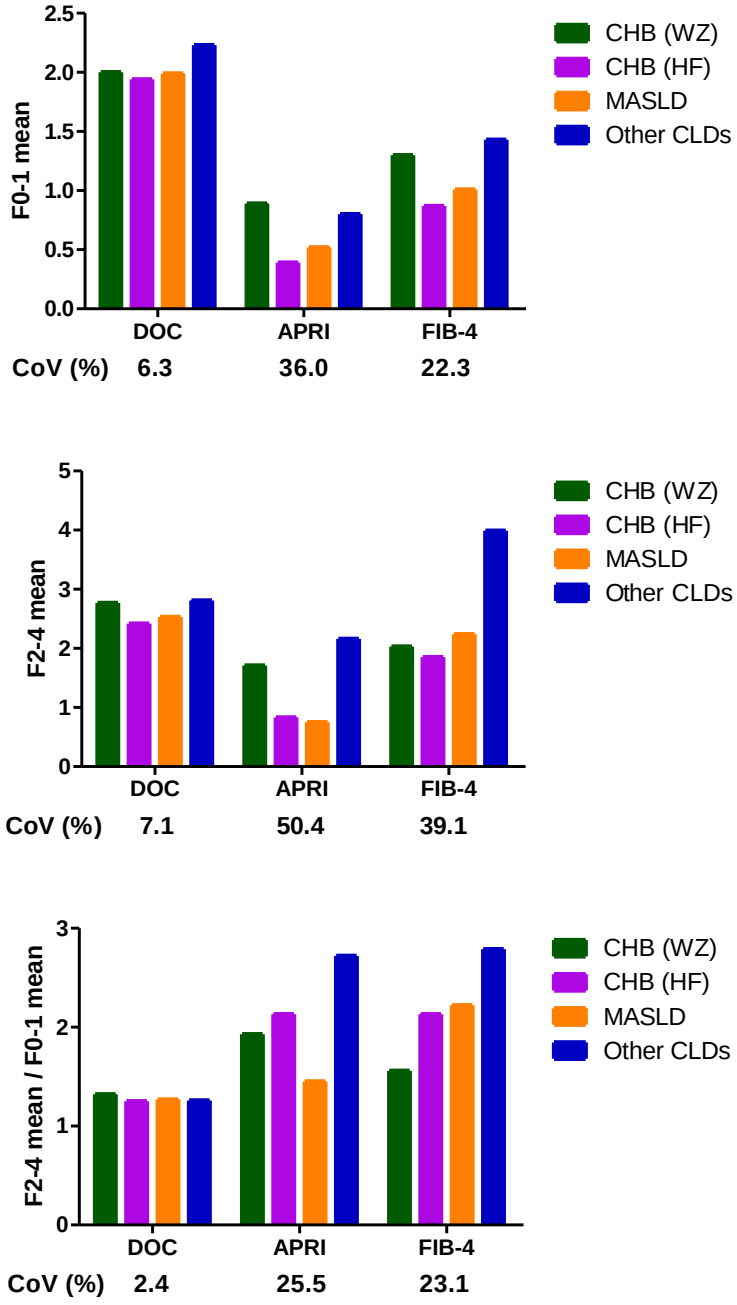

Fig. S1. F0-1 mean, F2-4 mean and F2-4 mean/F0-1 mean of DOC, APRI and FIB-4 in patient cohorts stratified by CLD etiology and the corresponding variability between cohorts.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; CoV, coefficient of variation; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index.

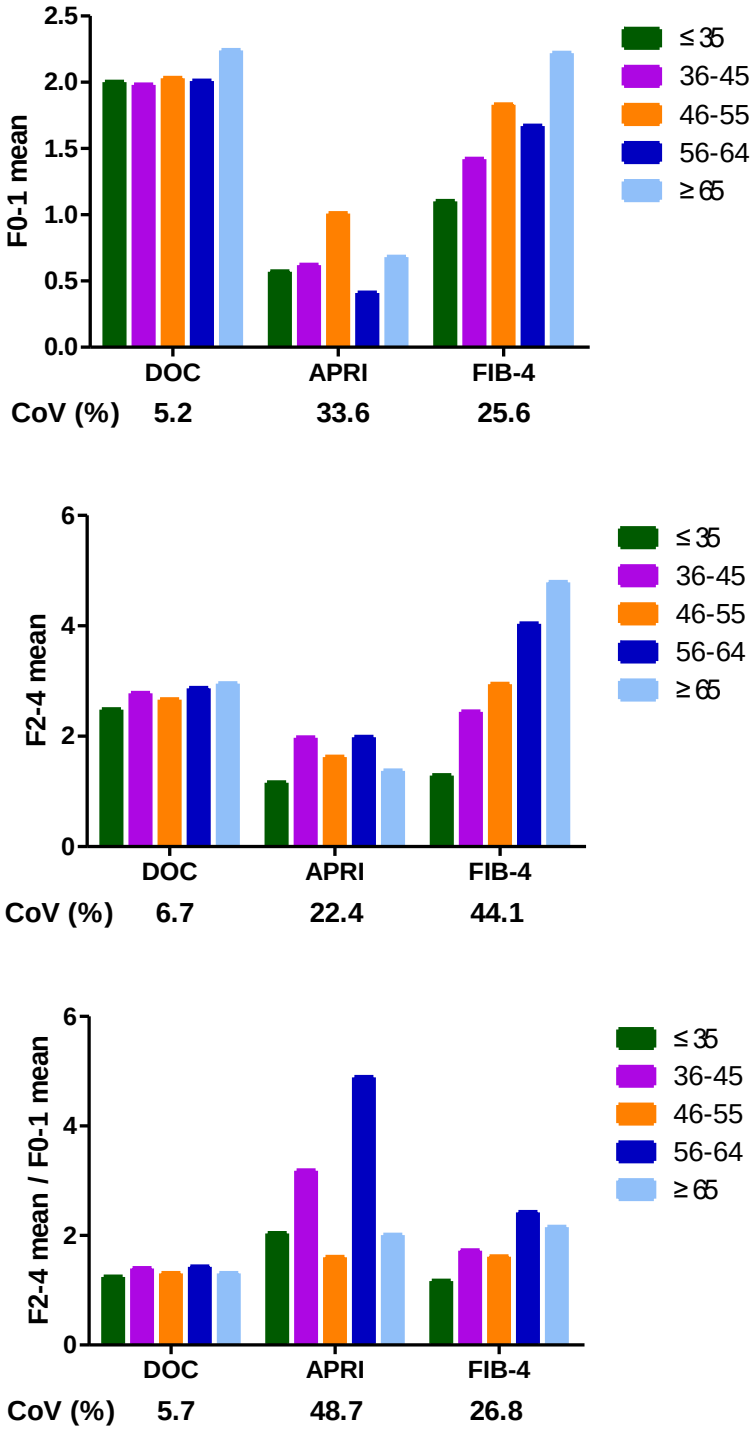

Fig. S2. F0-1 mean, F2-4 mean and F2-4 mean/F0-1 mean of DOC, APRI and FIB-4 in pooled CLD cohorts stratified by age and the corresponding variability between cohorts.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; CoV, coefficient of variation; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index.

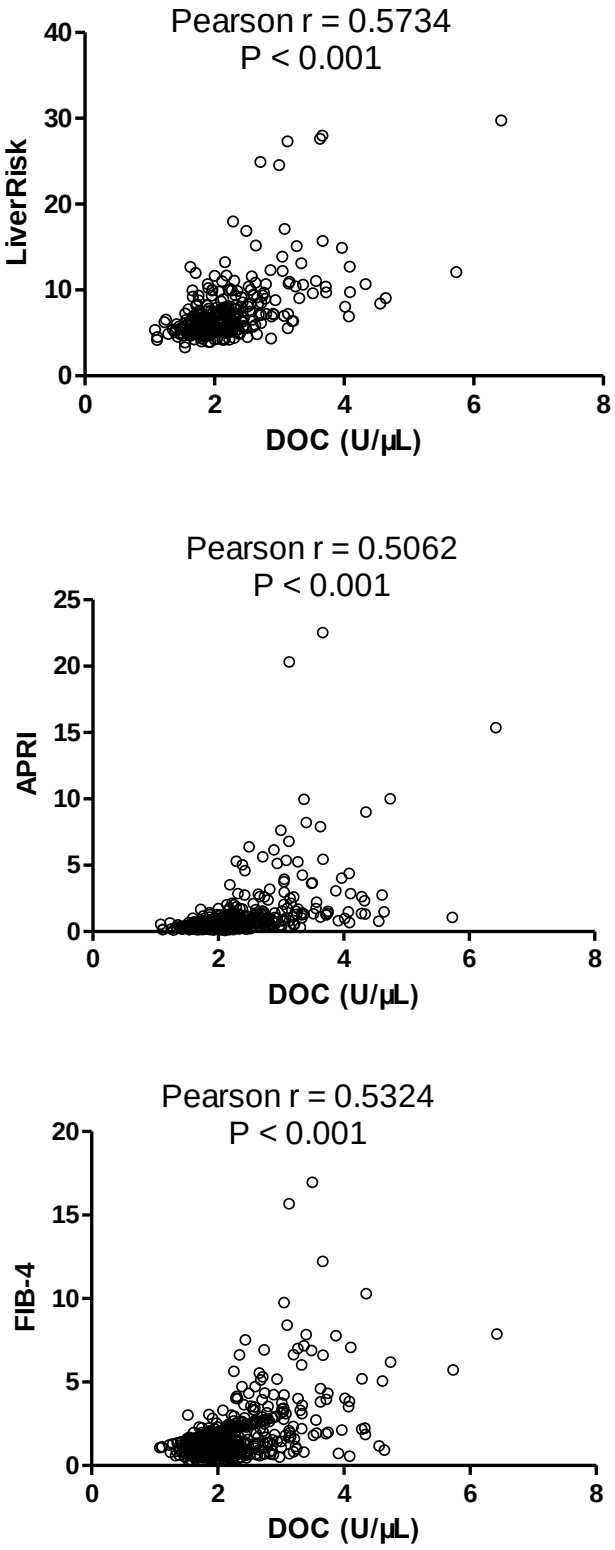

Fig. S3. Univariable linear correlations of DOC with LiverRisk, APRI or FIB-4 scores. A total of 325 CLD patients (203 from CHB (WZ) plus 122 from MASLD) with LiverRisk scores available were used for the analysis. All CLD patients (n=552) with FIB-4 and APRI data were used for the analysis.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; DOC, dithiothreitol-oxidizing capacity; FIB-4, fibrosis-4 index.