Prognostic performance of 7 biomarkers compared to liver biopsy in early alcohol-related liver disease

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Definitions of liver-related events and hospitalization for infection

Definition of liver related events

- Alcoholic hepatitis defined by recent onset of jaundice not explained by other factors and a corresponding hyperbilirubinemia above 50 µmol/L in a patient with ongoing or recent alcohol abuse.[1]
- Varices needing treatment defined as large varices or varices with bleeding stigmata on endoscopy.
- Variceal bleeding verified by endoscopy as bleeding from esophageal or gastric varices.[2]
- Ascites verified by any imaging modality.[3]
- SBP defined as >250 polymorphonucleated cells per µL of ascites with or without a positive fluid culture.[2]
- HE divided into overt HE, corresponding to grade 2 to 4 using the West Haven criteria, or covert HE diagnosed by psychometric measures: the Psychometric Hepatic Encephalopathy Score and the continuous reaction time test.[4-6]
- HCC diagnosed according to the LI-RADS classification.[7]
- HRS according to the HRS-AKI criteria, as acute kidney injury that does not respond to withdrawal of diuretics and volume expansion.[2]
- Upper gastrointestinal bleeding as gastroscopy-verified bleeding, not caused by varices.
- Jaundice defined by hyperbilirubinemia above 85 µmol/L or 5 mg/dL.[2]

Definition of hospitalization for infection

- An in-patient hospital stay for more than 24 hours with a positive blood culture or suspected infection based on clinical and paraclinical findings, which required the administration of antibiotics, antifungal or antiviral medicine.

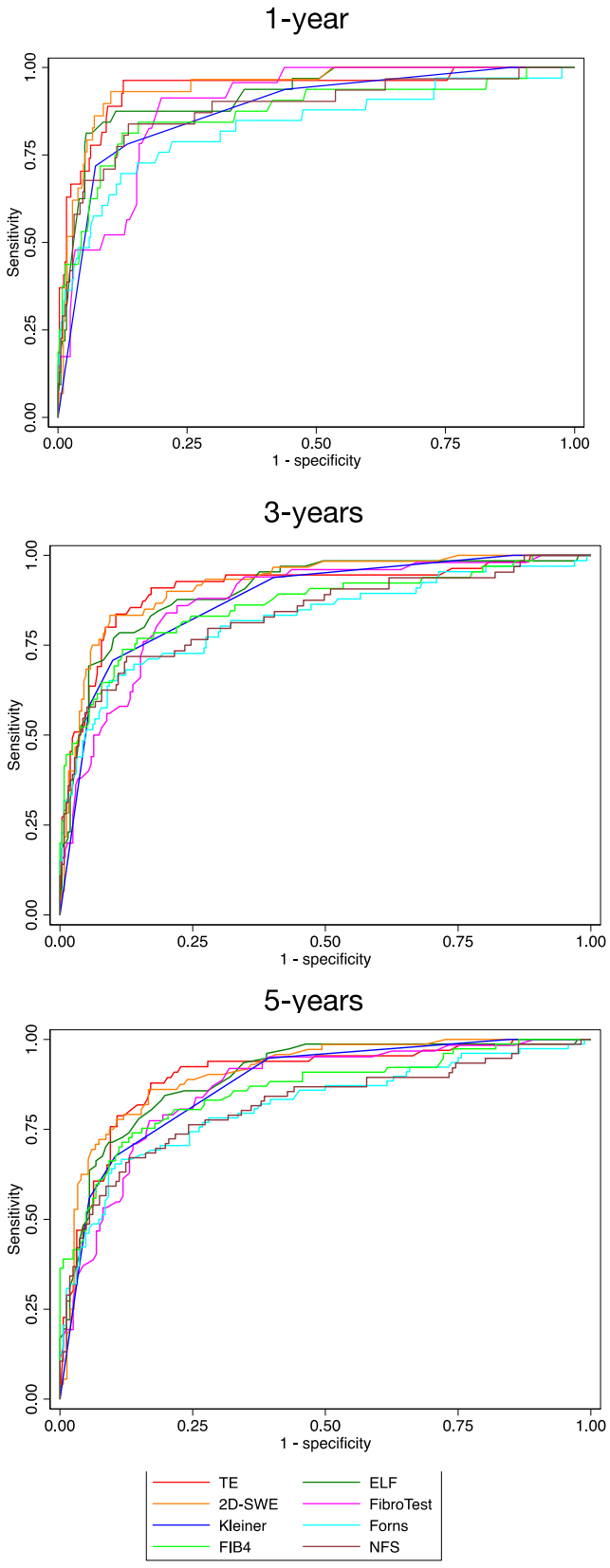
1-year
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - specificity
3-years
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - specificity
5-years
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - specificity
TE
2D-SWE
Kleiner
FIB4
ELF
FibroTest
Forns
NFS

Fig. S1. AUC for liver-related events within 1, 3 and 5 years**.** Receiver operating characteristics curves depicting the diagnostic accuracy of seven non-invasive tests and Kleiner liver fibrosis stage to predict liver-related events during 1 year (TOP), 3 years (MIDDLE) and 5 years (BOTTOM).

Abbreviations: 2D-SWE, 2-dimensional shear-wave elastography; AUC, area under the receiver operating characteristics curve; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; NFS non-alcoholic fatty liver disease fibrosis score; TE, transient elastography.

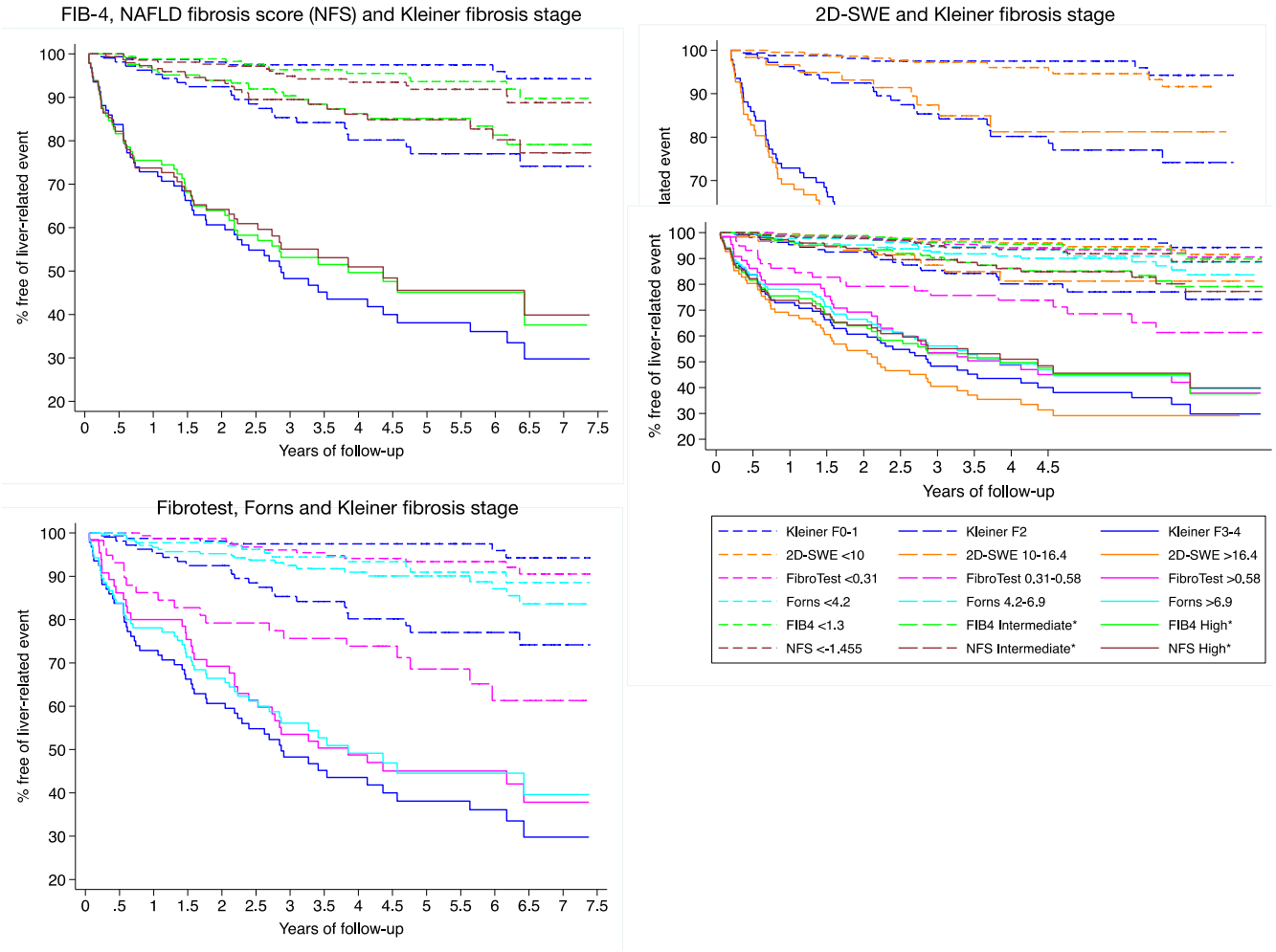

Fig. S2. Kaplan-Meier curves for liver-related events according to three groups of high, intermediate, and low risk. The curves for the histological kleiner fibrosis score in dark blue are plotted in the same panels at the non-invasive tests. The legend shows the cut-points used for each test.
(TOP LEFT) Fibrosis-4 index (FIB-4) and NAFLD fibrosis score (NFS)
(TOP RIGHT) 2-dimensional shearwave elastography (2D-SWE)
(LOWER LEFT) Fibrotest and Forns

Table S1. Individual liver-related events.

Patient#	AH	Ascites	cHE	oHE	HCC	HRS	Large varices	SBP	Variceal bleeding	Upper bleeding	Jaundice
1				X							
2				X						X	
3			X								
4	X	X									
5					X						
6										X	
7		X									
8							X		X		
9	X	X					X		X		
10							X				
11			X								
12			X								
13			X								
14					X						
15	X	X		X		X	X		X		
16					X						
17		X									
18		X		X							
19	X	X									
20					X	X					
21							X		X		
22	X										
23				X							
24							X				
25							X				
26		X		X		X					
27			X								
28		X									
29			X								
30		X									
31		X		X							
32		X									
33			X								
34		X									
35			X								
36				X							
37			X								
38		X		X					X		
39		X									
40			X								
41										X	
42		X					X		X		
43		X									

44	X										
45	X			X		X					
46		X									
47			X								
48		X					X				
49			X								
50	X										
51							X		X		
52		X									
53							X				
54		X		X							
55				X							
56								X			
57		X									
58					X						
59										X	
60									X		
61										X	
62		X									
63	X										
64		X		X		X				X	
65		X									
66				X			X		X	X	
67		X									
68		X									
69	X	X						X			
70										X	
71										X	
72	X										
73							X				
74			X								
75			X								
76					X						
77		X									
78		X									
79		X					X				
80										X	
81							X				
82			X								
83											
84										X	

Eighty-four patients experienced a liver-related event, which is a composite outcome of ten different clinical complications. The table shows the individual events that caused each of the 84 patients to have a liver-related event. The table shows only the patients' first instance of liver-related event. Abbreviations: AH, alcoholic hepatitis; cHE, covert hepatic encephalopathy; oHE, overt hepatic encephalopathy; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Table S2. Head-to-head comparison of prognostic accuracies in survival analyses.

	Harrell's C	TE	ELF	2D-SWE	FT	Forns	NFS	FIB-4
TE	0.876	*						
ELF	0.859	0.43	*					
2DS-WE	0.868	0.33	0.69	*				
FT	0.808	0.00	0.01	0.01	*			
Forns	0.783	0.00	0.01	0.00	0.14	*		
NFS	0.794	0.00	0.02	0.00	0.14	0.74	*	
FIB-4	0.821	0.04	0.12	0.05	0.59	0.09	0.07	*
Fibrosis stage	0.819	0.01	0.14	0.14	0.52	0.06	0.14	0.76

Prognostic accuracy according to Harrell's C, to predict liver-related events from univariate Cox regressions. With pairwise p-values for between-test comparisons according to Somers' D, for comparison of the tests' predictive strength.

Table S3. Prognostic performance within the timeframes of 1, 3 and 5 years

	AUC at 1 year	AUC at 3 years	AUC at 5 years
TE	0.917 (0.858-0.975)	0.893 (0.841-0.946)	0.890 (0.842-0.938)
ELF	0.888 (0.834-0.942)	0.888 (0.843-0.933)	0.890 (0.847-0.933)
2D-SWE	0.913 (0.867-0.959)	0.911 (0.871-0.950)	0.909 (0.869-0.950)
FT	0.839 (0.775-0.902)	0.855 (0.800-0.910)	0.859 (0.807-0.912)
Forns	0.805 (0.717-0.894)	0.813 (0.748-0.879)	0.810 (0.747-0.873)
NFS	0.852 (0.777-0.928)	0.826 (0.763-0.889)	0.812 (0.748-0.876)
FIB-4	0.840 (0.758-0.921)	0.852 (0.793-0.911)	0.855 (0.800-0.910)
Fibrosis stage	0.843 (0.777-0.909)	0.858 (0.812-0.905)	0.868 (0.823-0.912)

Prognostic accuracy with 95% confidence intervals for seven non-invasive tests and histological fibrosis stage to predict liver-related events. The prognostic accuracy is reported as the area under the receiver operating characteristics curve for liver-related events within 1, 3 and 5 years.

Abbreviations: 2D-SWE, 2-dimensional shear-wave elastography; AUC, area under the receiver operating characteristics curve; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; NFS non-alcoholic fatty liver disease fibrosis score; TE, transient elastography.

Table S4. Head-to-head comparisons of prognostic accuracies of predicting liver-related events within the timeframes of 1, 3 and 5 years

AUC for liver-related events within 1 year								
	AUC	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**FIB-4**
TE	0.917	*						
ELF	0.888	0.56	*					
2D-SWE	0.913	0.15	0.43	*				
FT	0.839	0.00	0.04	0.00	*			
Forns	0.805	0.03	0.14	0.00	0.81	*		
NFS	0.852	0.21	0.47	0.05	0.88	0.21	*	
FIB-4	0.840	0.20	0.28	0.07	0.55	0.57	0.49	*
Fibrosis stage	0.843	0.00	0.17	0.08	0.87	0.27	0.97	0.80
AUC for liver-related events within 3 years								
	AUC	TE	ELF	2D-SWE	FT	Forns	NFS	FIB-4
TE	0.893	*						
ELF	0.888	0.70	*					
2D-SWE	0.911	0.51	0.65	*				
FT	0.855	0.00	0.09	0.03	*			
Forns	0.813	0.01	0.02	0.00	0.18	*		
NFS	0.826	0.02	0.05	0.01	0.19	0.79	*	
FIB-4	0.852	0.14	0.22	0.08	0.53	0.20	0.11	*
Fibrosis stage	0.858	0.03	0.19	0.11	0.91	0.15	0.34	0.93
AUC for liver-related events within 5 years								
	AUC	TE	ELF	2D-SWE	FT	Forns	NFS	FIB-4
TE	0.890	*						
ELF	0.890	0.90	*					
2D-SWE	0.909	0.44	0.98	*				
FT	0.859	0.01	0.07	0.12	*			
Forns	0.810	0.00	0.01	0.00	0.05	*		
NFS	0.812	0.00	0.01	0.00	0.04	0.99	*	
FIB-4	0.855	0.10	0.16	0.07	0.41	0.08	0.01	*
Fibrosis stage	0.868	0.05	0.19	0.23	0.85	0.05	0.09	0.69

The second column shows AUC, which is the test statistic for prognostic performance within each of the timeframes of 1, 3 and 5 years. The columns to the right thereof show a matrix of *P*-values for each individual comparison of the predictive strength of the tests. A *P*-value below 0.05 indicates that two tests have a different prognostic strength.

Table S5. Head-to-head comparisons of the ability to predict all-cause mortality and hospitalizations for infections.

Univariate Cox regressions for all-cause mortality								
	Harrell's C	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**Fib-4**
TE	0.757	*						
ELF	0.758	0.83	*					
2D-SWE	0.714	0.25	0.08	*				
FT	0.721	0.56	0.33	0.81	*			
Forns	0.701	0.05	0.04	0.24	0.07	*		
NFS	0.657	0.00	0.00	0.02	0.02	0.06	*	
Fib-4	0.705	0.11	0.09	0.31	0.20	0.71	0.02	*
Fibrosis stage	0.699	0.13	0.02	0.39	0.47	0.91	0.22	0.99
Univariate Cox regressions for hospitalizations for infections								
	Harrell's C	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**FIB-4**
TE	0.677	*						
ELF	0.672	0.87	*					
2D-SWE	0.660	0.29	0.43	*				
FT	0.645	0.24	0.09	0.34	*			
Forns	0.621	0.04	0.02	0.04	0.11	*		
NFS	0.594	0.00	0.01	0.00	0.13	0.24	*	
Fib-4	0.609	0.02	0.01	0.05	0.02	0.47	0.74	*
Fibrosis stage	0.638	0.05	0.03	0.06	0.66	0.42	0.19	0.32

The second column shows Harrell's C for the outcomes of all-cause mortality and hospitalizations for infections. The columns to the right thereof show a matrix of p-values for each individual comparison of the tests' predictive strength. A *P*-value below 0.05 indicates that two tests have a different prognostic strength.

Table S6. Three risk groups with adjustment for age, gender, BMI and type 2 diabetes.

	Risk groups	Events/patients in group (%)	Hazard ratio	*P* value
TE (kPa)				
	<10	9/303 (3%)	1	-
	10-15	9/42 (21%)	8.75 (3.47-22.11)	< 0.001
	>15	53/98 (54%)	28.02 (13.56-57.91)	0.002
ELF				
	<9.8	15/300 (5%)	1	-
	9.8-10.5	11/49 (22%)	4.94 (2.20-11.08)	<0.001
	>10.5	57/108 (53%)	17.56 (9.58-32.19)	<0.001
2D-SWE (kPA)				
	<10	12/222 (5%)	1	-
	10-16.4	9/60 (15%)	3.8 (1.59- 9.08)	0.003
	>16.4	53/83 (64%)	22.06 (11.44-42.54)	<0.001
FibroTest				
	<0.31	12/157 (8%)	1	-
	0.31-0.58	19/59 (32%)	6.2 (2.90-13.28)	<0.001
	>0.58	37/67 (55%)	14.1 (6.84-29.09)	0.005
Forns index				
	<4.2	11/135 (8%)	1	-
	4.2-6.9	22/214 (10%)	1.8 (0.83- 3.90)	0.138
	>6.9	51/106 (48%)	12.15 (5.78-25.54)	<0.001
NFS				
	Low	16/191 (8%)	1	-
	Intermediate	22/175 (13%)	2.87 (1.42- 5.84)	0.003
	>0.676	42/66 (64%)	29.67 (14.79-59.52)	< 0.001
FIB-4				
	Low	11/170 (6%)	1	-
	Intermediate	15/156 (10%)	1.92 (0.85- 4.36)	<0.117
	>2.67	56/103 (54%)	14.28 (7.13-28.60)	<0.001
Fibrosis stage				
	F0-1	6/162 (4%)	1	-
	F2	22/107 (21%)	6.66 (2.68-16.55)	<0.001
	F3-4	55/94 (59%)	26.08 (10.96-62.03)	< 0.001

Risk of liver-related events for three risk groups defined by test-specific cut-offs adjusted for age, gender, BMI and type 2 diabetes This model is adjusted for age, gender, BMI and type 2 diabetes. Compare with table 3 that shows unadjusted hazard ratios from univariate Cox regressions.

Table S7. Three risk groups with adjustment for age, gender, BMI, type 2 diabetes and excess drinking during follow-up.

	Risk groups	Events/patients in group (%)	Hazard ratio	*P* value
TE (kPa)				
	<10	9/303 (3%)	1	-
	10-15	9/42 (21%)	8.33 (3.30-21.07)	<0.001
	>15	53/98 (54%)	29.28 (14.20-60.40)	0.001
ELF				
	<9.8	15/300 (5%)	1	-
	9.8-10.5	11/49 (22%)	4.77 (2.13-10.67)	0.001
	>10.5	57/108 (53%)	18.97 (10.32-34.88)	0.001
2D-SWE (kPA)				
	<10	12/222 (5%)	1	-
	10-16.4	9/60 (15%)	3.64 (1.52- 8.72)	0.004
	>16.4	53/83 (64%)	23.67 (12.27-45.65)	0.001
FibroTest				
	<0.31	12/157 (8%)	1	-
	0.31-0.58	19/59 (32%)	6.14 (2.88-13.11)	0.001
	>0.58	37/67 (55%)	13.93 (6.79-28.58)	0.005
Forns index				
	<4.2	11/135 (8%)	1	-
	4.2-6.9	22/214 (10%)	1.67 (0.76- 3.67)	<0.199
	>6.9	51/106 (48%)	11.49 (5.45-24.23)	<0.001
NFS				
	Low	16/191 (8%)	1	-
	Intermediate	22/175 (13%)	2.8 (1.37- 5.71)	0.005
	>0.676	42/66 (64%)	28.48 (14.17-57.26)	<0.001
FIB-4				
	Low	11/170 (6%)	1	-
	Intermediate	15/156 (10%)	1.85 (0.81- 4.22)	0.143
	>2.67	56/103 (54%)	13.83 (6.87-27.83)	<0.001
Fibrosis stage				
	F0-1	6/162 (4%)	1	-
	F2	22/107 (21%)	6.37 (2.56-15.84)	<0.001
	F3-4	55/94 (59%)	27.7 (11.64-65.95)	0.001

Risk of liver-related events for three risk groups defined by test-specific cut-offs adjusted for age, gender, BMI, type 2 diabetes and excess drinking during follow-up. This model is adjusted for age, gender, BMI, type 2 diabetes and excessive drinking during follow-up. Compare with table 3 that shows unadjusted hazard ratios from univariate Cox regressions.

Table S8. Prognostic performance with the endpoint of decompensations

	Survival analyses (Harrell's C)	Prognostic analyses (AUC)		
		1 year	3 years	5 years
TE	0.865 (0.820-0.911)	0.911 (0.869-0.954)	0.888 (0.831-0.944)	0.875 (0.822-0.928)
ELF	0.844 (0.794-0.893)	0.876 (0.795-0.956)	0.854 (0.792-0.916)	0.872 (0.820-0.924)
2D-SWE	0.845 (0.797-0.894)	0.873 (0.786-0.960)	0.878 (0.822-0.933)	0.869 (0.815-0.923)
FT	0.773 (0.716-0.831)	0.812 (0.714-0.910)	0.794 (0.716-0.871)	0.824 (0.759-0.889)
Forns	0.722 (0.649-0.795)	0.701 (0.550-0.853)	0.737 (0.649-0.826)	0.754 (0.676-0.832)
NFS	0.727 (0.653-0.801)	0.772 (0.631-0.913)	0.728 (0.634-0.821)	0.750 (0.667-0.833)
FIB-4	0.755 (0.684-0.826)	0.761 (0.614-0.908)	0.763 (0.675-0.852)	0.793 (0.719-0.867)
Fibrosis stage	0.790 (0.740-0.841)	0.786 (0.692-0.880)	0.822 (0.761-0.884)	0.832 (0.776-0.888)

This table shows the prognostic abilities for the eight tests to predict the more restrictive endpoint of decompensation of liver disease. A decompensation could be overt HE, variceal bleeding, major ascites requiring parascentesis or jaundice.
The second column shows Harrell's C with 95% confidence intervals from univariate Cox regressions. The three columns to the right show the area under the receiver operating characteristics curve for decompensation within the timeframes of 1, 3 and 5 years.

Table S9. Head-to-head comparisons for the endpoint of decompensations

Harrell's C for decompensations								
	Harrell's C	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**FIB-4**
TE	0.866	*						
ELF	0.844	0.81	*					
2D-SWE	0.846	0.46	1.00	*				
FT	0.774	0.01	0.02	0.00	*			
Forns	0.723	0.00	0.00	0.00	0.07	*		
NFS	0.727	0.00	0.00	0.00	0.05	0.99	*	
FIB-4	0.755	0.00	0.01	0.00	0.14	0.33	0.21	*
Fibrosis stage	0.791	0.02	0.10	0.21	0.55	0.02	0.03	0.21
AUC for decompensations within 1 year								
	AUC	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**Fib-4**
TE	0.911	*						
ELF	0.876	0.92	*					
2D-SWE	0.874	0.32	0.85	*				
FT	0.813	0.24	0.27	0.05	*			
Forns	0.702	0.01	0.04	0.00	0.28	*		
NFS	0.772	0.08	0.21	0.06	0.57	0.29	*	
FIB-4	0.761	0.13	0.14	0.10	0.21	0.61	0.66	*
Fibrosis stage	0.787	0.01	0.03	0.05	0.73	0.18	0.83	0.70
AUC for decompensations within 3 years								
	AUC	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**FIB-4**
TE	0.888	*						
ELF	0.854	0.39	*					
2D-SWE	0.878	0.59	0.52	*				
FT	0.794	0.01	0.09	0.00	*			
Forns	0.738	0.00	0.01	0.00	0.21	*		
NFS	0.727	0.00	0.00	0.00	0.09	0.60	*	
FIB-4	0.764	0.00	0.02	0.01	0.19	0.63	0.18	*
Fibrosis stage	0.823	0.07	0.39	0.20	0.58	0.04	0.04	0.23
AUC for decompensations within 5 years								
	AUC	**TE**	**ELF**	**2D-SWE**	**FT**	**Forns**	**NFS**	**FIB-4**
TE	0.875	*						
ELF	0.871	0.60	*					
2D-SWE	0.869	0.55	0.41	*				
FT	0.824	0.07	0.03	0.10	*			
Forns	0.754	0.00	0.00	0.00	0.02	*		
NFS	0.750	0.00	0.00	0.00	0.04	0.80	*	
FIB-4	0.793	0.02	0.01	0.02	0.13	0.19	0.04	*
Fibrosis stage	0.832	0.06	0.08	0.44	0.80	0.03	0.05	0.33

This table shows head-to-head comparisons for the prognostic abilities for the eight tests to predict the more restrictive endpoint of decompensation. A decompensation could be overt HE, variceal bleeding, major ascites requiring parascentesis or jaundice.
The second column shows the test statistic for prognostic performance – either Harrell's C from univariate Cox regressions or AUC – for the outcome of liver-related event. The columns to the right thereof show a matrix of *P*-values for each individual comparison of the predictive strength of the tests. A *P*-value below 0.05 indicates that two tests have a different prognostic strength.

Table S10. Calculations of FIB-4, NFS and Forns index

Test	Calculation
FIB-4	(age*AST)/(plates*ALT)
NFS	NAFLD Score = -1.675 + (0.037*age [years]) + (0.094*BMI [kg/m^2]) + (1.13*IFG/diabetes [yes = 1, no = 0]) + (0.99*AST/ALT ratio) – (0.013*platelet count [×10^9/L]) – (0.66*albumin [g/dl])
Forns	7.811 - 3.131*ln(platelets) + 0.781*ln(GGT) + 3.467*ln(age) - 0.541*(chol[1])
[1]Chol is cholesterole in mmol/L.	

Table S11. Tripod checklist

Section/Topic	ı	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title page not fully covering, page 1.
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract not fully covering, page 5
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Yes, see first part of introduction, page 7.
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	Yes, see last part of introduction, page 7.
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	See subsection Study design of the methods section, page 9. Source of follow-up date described in subsection Follow-up and outcome assessment, page 11.
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	For dates of inclusion of patients see the subsection Patients in the results section, page 14. For date of end of follow-up: see subsection Follow-up and outcome assessment in the methods section, p 11
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	See subsection Patients in the methods section, page 9. This was a single center study
	5b	Describe eligibility criteria for participants.	See subsection Patients in the methods section, page 8.
	5c	Give details of treatments received, if relevant.	Not relevant.
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	See the subsection Follow-up and outcome assessment of the methods section, page 11.
	6b	Report any actions to blind assessment of the outcome to be predicted.	Not performed.

Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	See the subsections, Non-invasive tests and liver biopsy in the methods section, page 10.
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	Assessment of biopsies were blinded. See subsection non-invasive tests and liver biopsy in the methods section, page 10.
Sample size	8	Explain how the study size was arrived at.	All consecutive patients with an available follow-up was used.
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	We used complete case analysis. See subsection Statistics in Methods section, page 12.
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	Some predictors were calculated based on laboratory results. See supplementary table 10.
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Harrell's C from univariate Cox regressions and prognostic AUC derived from univariate logistic regressions. See subsections Statistics in methods section, page 12.
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	Not relevant
Risk groups	11	Provide details on how risk groups were created, if done.	See subsection Risk groups in methods section, page 10.
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Not addressed. All of the cut offs we validate were developed in either NAFLD or ALD.
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	See the two sub sections Patients and Follow-up in methods in the Results section, page 14. Also see table 1.
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	See table 1. Number of patients with missing data can be calculated from numbers given in table 3.
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Not performed

Model performance	16	Report performance measures (with CIs) for the prediction model.	For the main performance measures see table 2, and additional information in supplementary table 3.
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	No updating done.
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	See page 20-
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Not done.
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	See page 18
Implications	20	Discuss the potential clinical use of the model and implications for future research.	See page 28
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	We have no supplementary resources
Funding	22	Give the source of funding and the role of the funders for the present study.	Yes, we describe this on the title page.

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