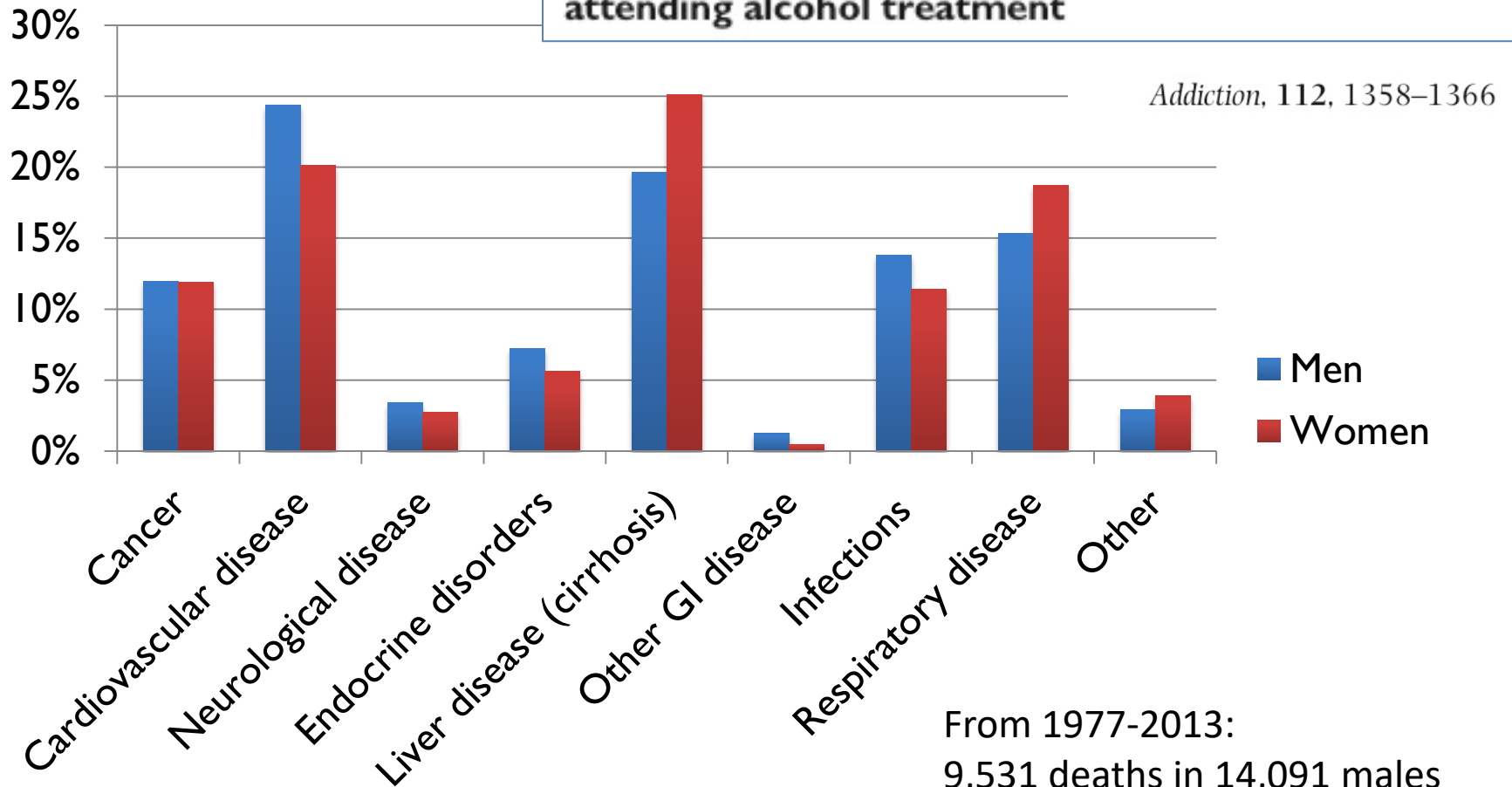


Nye metoder til tidlig opsporing af alkoholisk leversygdom

Maja Thiele, Ph.D., associate professor

Odense University Hospital and University of Southern Denmark

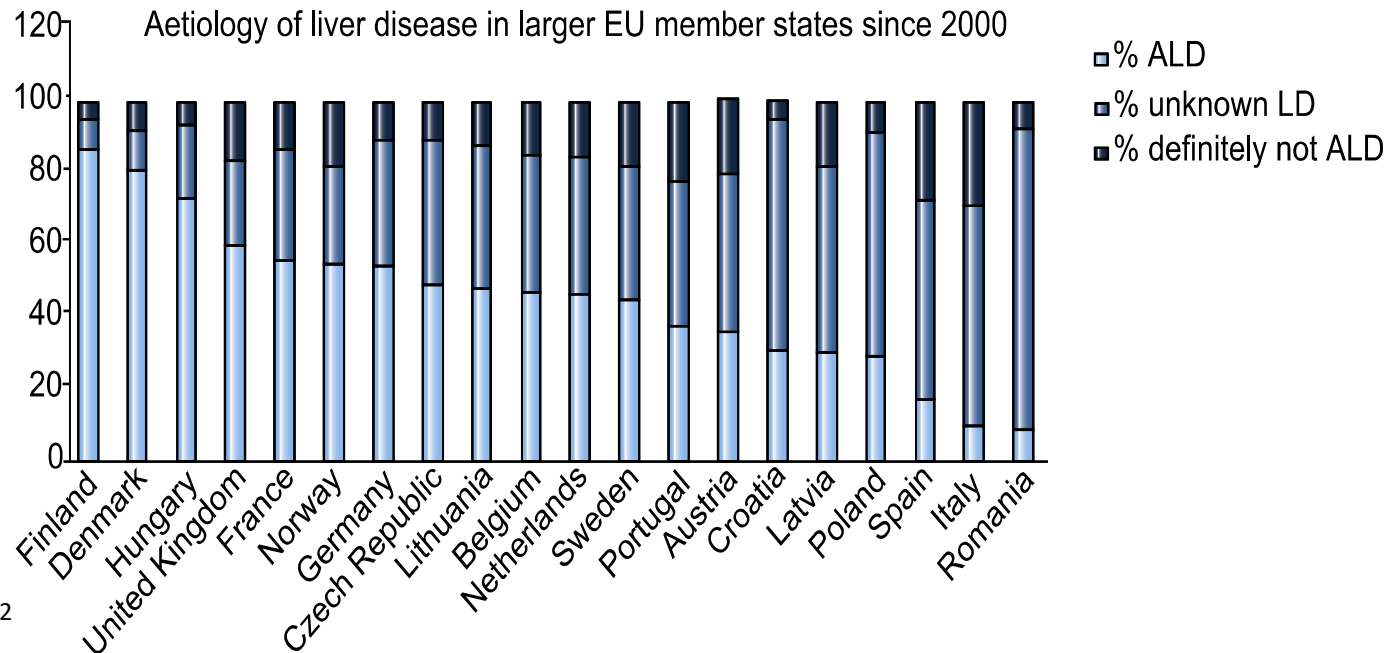
Alcohol dependence and risk of somatic diseases and mortality: a cohort study in 19002 men and women attending alcohol treatment



From 1977-2013:
9,531 deaths in 14,091 males
2,693 deaths in 4,911 females

Problemet: Alkohol

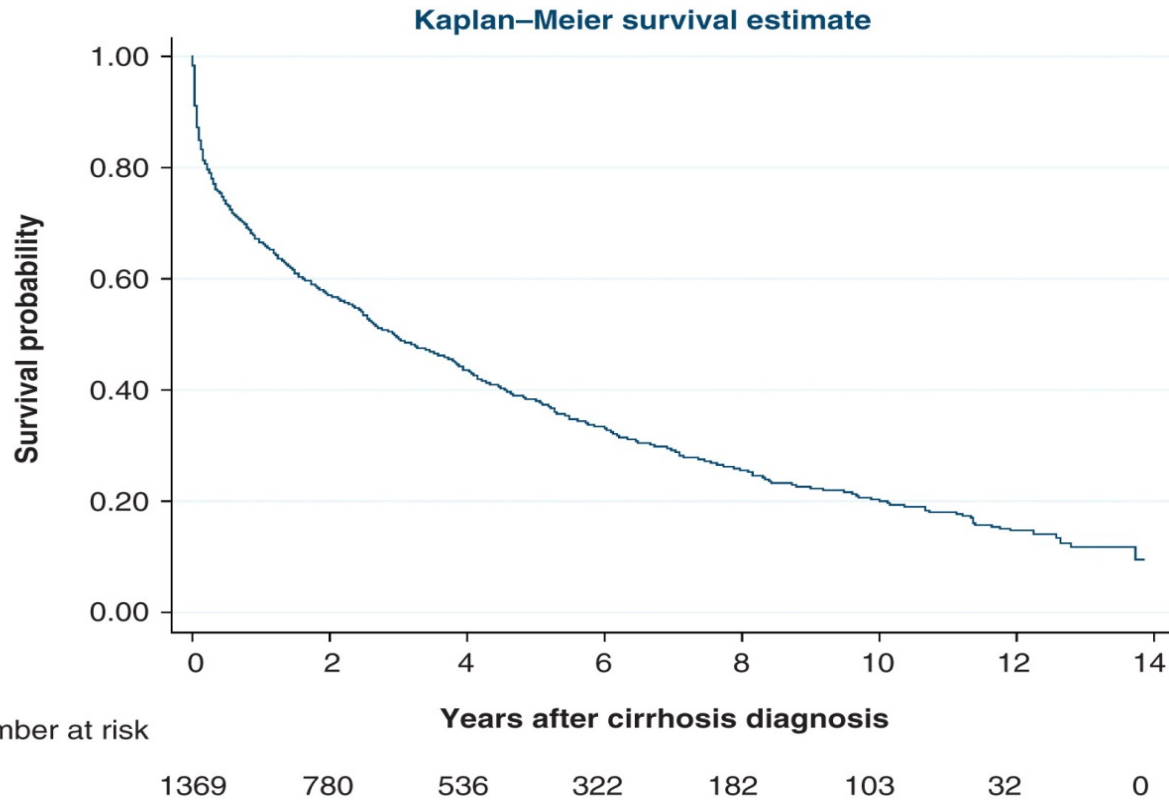
- Europe er verdensmestre i alkoholforbrug¹
- Alkohol er årsag til halvdelen af alle skrumpeliver-dødsfald i verden¹
- Tre ud af fire patienter bliver først diagnosticeret når sygdommen er meget fremskreden²



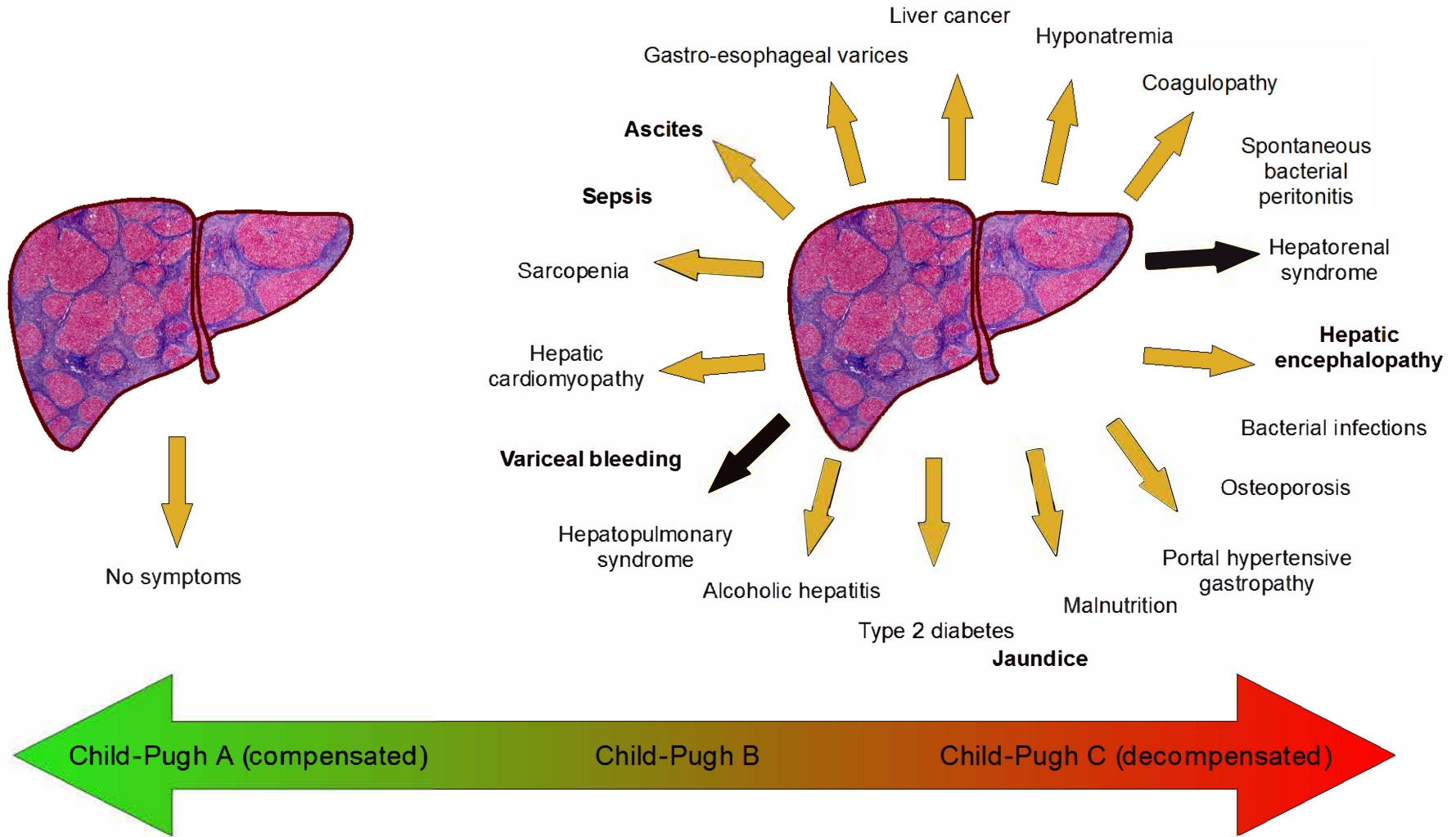
1: Sheron, J Hep 2016, 64:957-967

2: Jepsen, Hepatology 2010, 51(5):1675-82

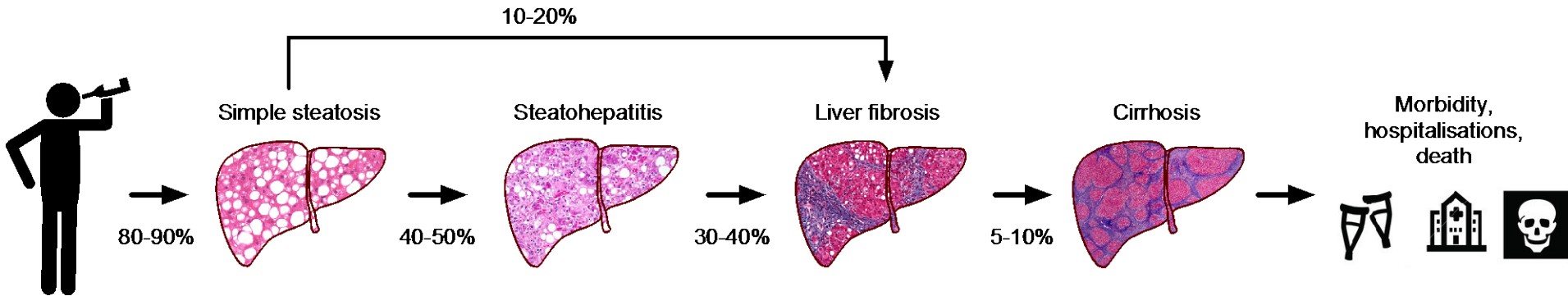
20 år uden symptomer, 3 år med



Fialla, Scand J Gastroent 2012



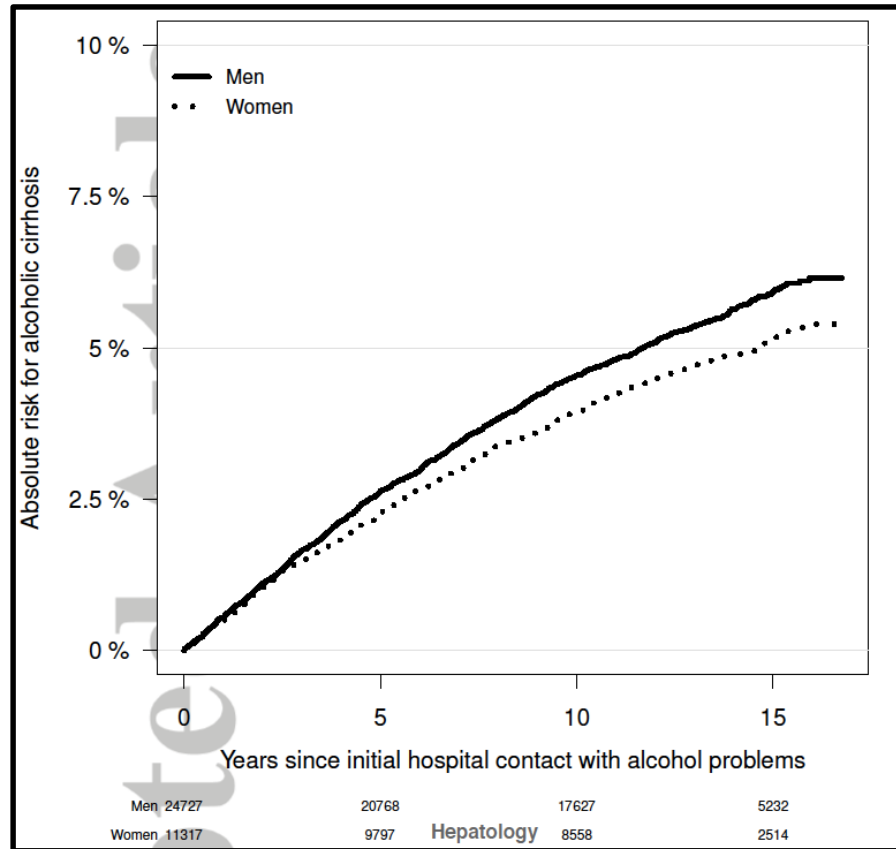
Alkoholisk leversygdom



Resultat: Omtrent 1/50
danskere med et alkohol-
overforbrug udvikler
cirrose!



Gro Askgaard online Hepatology



Omfanget af det danske alkoholproblem



Nogle diagnoser er lette

51 year old male, quit drinking 4 weeks ago

Prior to that: 15 years excessive drinking, up to 25 units/day

- BMI 28. BP 133/83
- Albumin = 44 g/L
- ALT = 74 IU/L
- AST = 60 IU/L
- GGT = 150 IU/L
- Alk phosph. = 104 IU/L
- Bilirubin = 12 $\mu\text{mol/L}$
- INR = 1.0
- Platelets = 219 $10^9/\text{L}$

42 year old male, quit drinking 4 weeks ago

Prior to that: 25 years excessive drinking, up to 30 units/day

- BMI 29. BP 131/85
- = 44 g/L
- = 34 IU/L
- = 32 IU/L
- = 57 IU/L
- = 96 IU/L
- = 4 $\mu\text{mol/L}$
- = 1.0
- = 314 $10^9/\text{L}$

F4 vs F1

Hvad er problemet med de almindelige levertal?

	Øvre normalgrænse	AUROC	Sensitivitet	Specificitet
Basisk fosfatase	105 U/L	0.77	69%	75%
ALAT	70/45 U/L	0.54	9%	85%
ASAT	45/35 U/L	0.72	60%	73%
Bilirubin	25 µmol/L	0.75	29%	96%
GGT	115/75 U/L	0.71	64%	64%
INR	1.3	0.80	43%	96%
Trombocytter	350/400 10 ⁹ /L	0.76	5%	94%

Hansen & Lindvig, International Liver Congress 2018

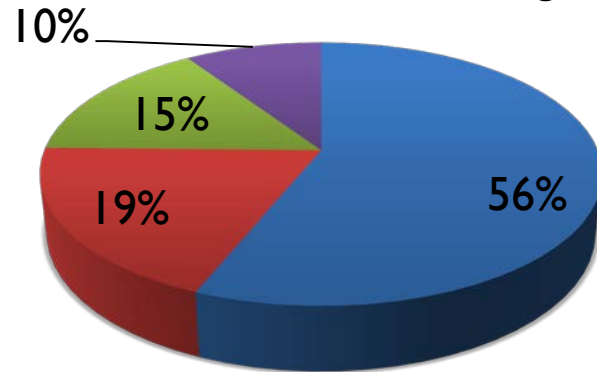
Hvad med de dygtige praktiserende læger?

Lever biopsi	Praksislæge 1		Praksislæge 2	
	Nej	Ja	Nej	Ja
F0-2 = 177	132	45 (25%)	169	8 (5%)
F3-4 = 58	22 (38%)	36	31 (53%)	27
	154	81	200	35

Hvad med de dygtige praktiserende læger?

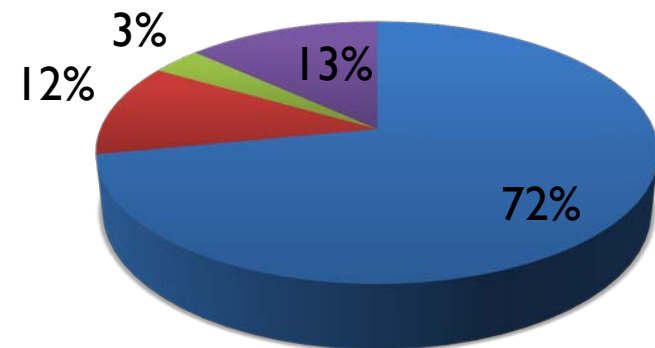
Læge 1

- Gætter rigtigt: Sandt negativ
- Gætter rigtigt: Sandt positiv
- Gætter forkert: Falsk positiv
- Gætter forkert: Falsk negativ



Læge 2

- Gætter rigtigt: Sandt negativ
- Gætter rigtigt: Sandt positiv
- Gætter forkert: Falsk positiv
- Gætter forkert: Falsk negativ

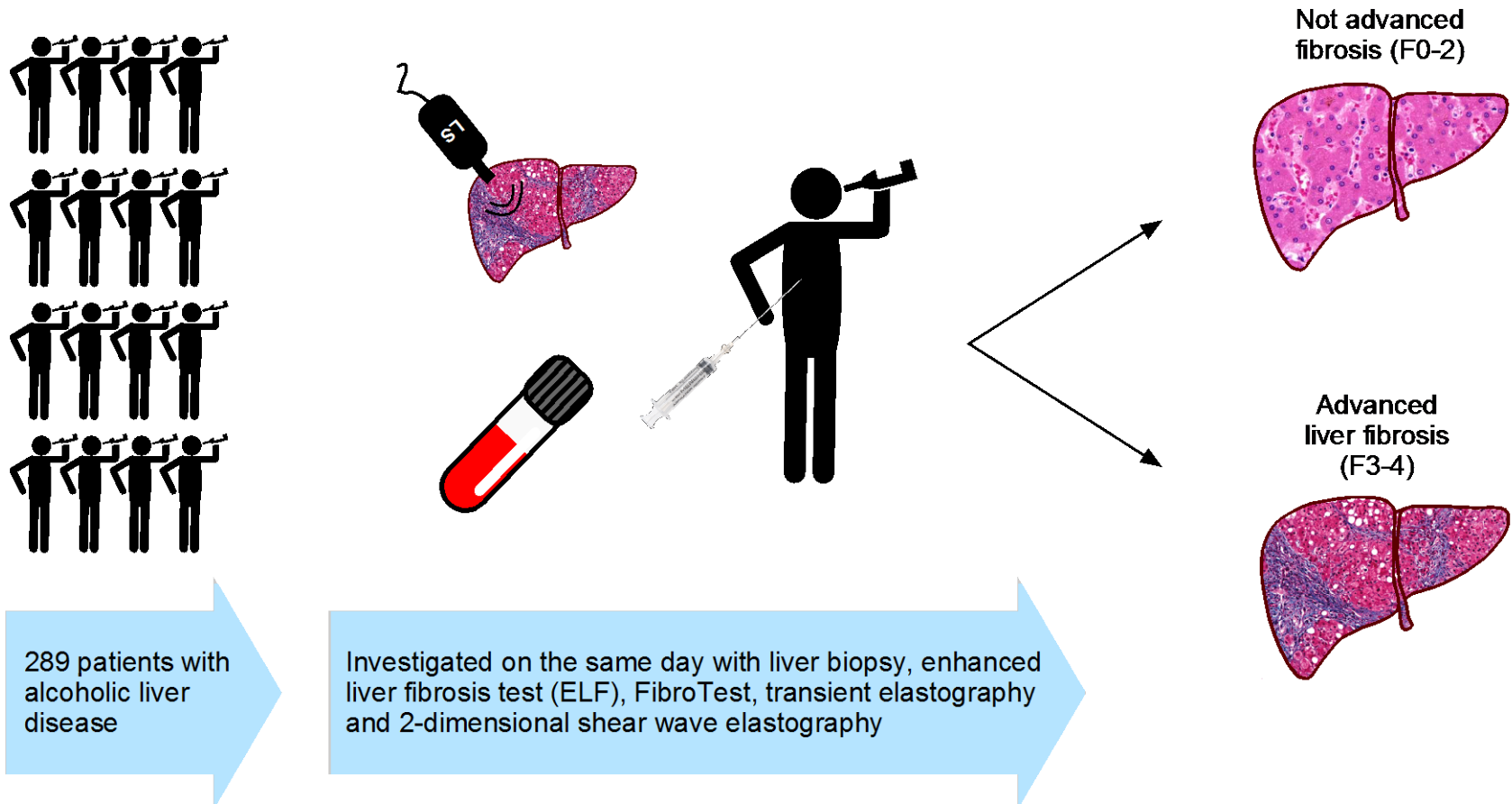


Hvad med de dygtige leverlæger?

Lever biopsi	Speciallæge		HU læge	
	Nej	Ja	Nej	Ja
F0-2 = 177	164	13 (7%)	162	15 (8%)
F3-4 = 58	20 (34%)	38	29 (50%)	29
	184	51	191	44

Der er brug for hjælp!

Leverfibrose-kohorten på OUH



Thiele, Gastroenterology 2016 and 2018

Tre nye metoder til tidlig opsporing af alkoholisk leversygdom:

- Indirekte fibrosemarkører = algoritmer af rutine-blodprøver
- Direkte fibrosemarkører = blodprøver, som måler på komponenter af leverfibrose
- Elastografi = stivhedsmåling af leveren vha. ultralyd eller MR skanning

Indirekte fibrosemarkører

	ALT	AST	Platelet count	Age	GGT	Chol.	Albumin	BMI	Diabetes
AST:ALT ratio ¹	✓	✓							
Age-platelet index ²			✓	✓					
APRI ³		✓	✓						
FIB-4 ⁴	✓	✓	✓	✓					
Forns index ⁵			✓	✓	✓	✓			
BARD ⁶	✓	✓						✓	✓
NAFLD fibrosis score ⁷	✓	✓	✓	✓			✓	✓	✓

1: Williams: Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988

2: Poynard: Age and platelet count: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. J Viral Hepat 1997

3: Wai: A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003

4: Sterling: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006

5: Forn: Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002

6: Harrison: Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008.

7: Angulo et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007.

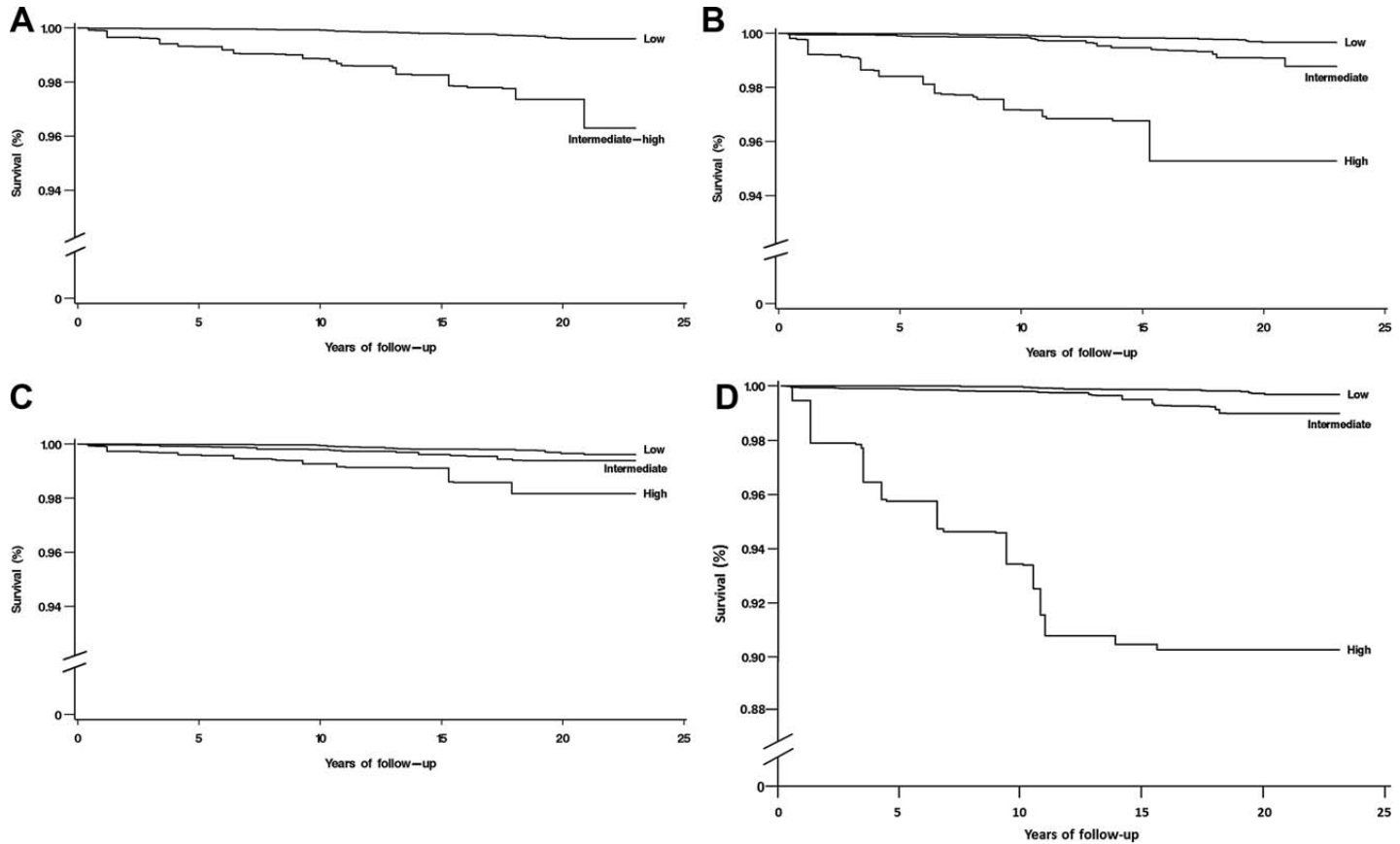
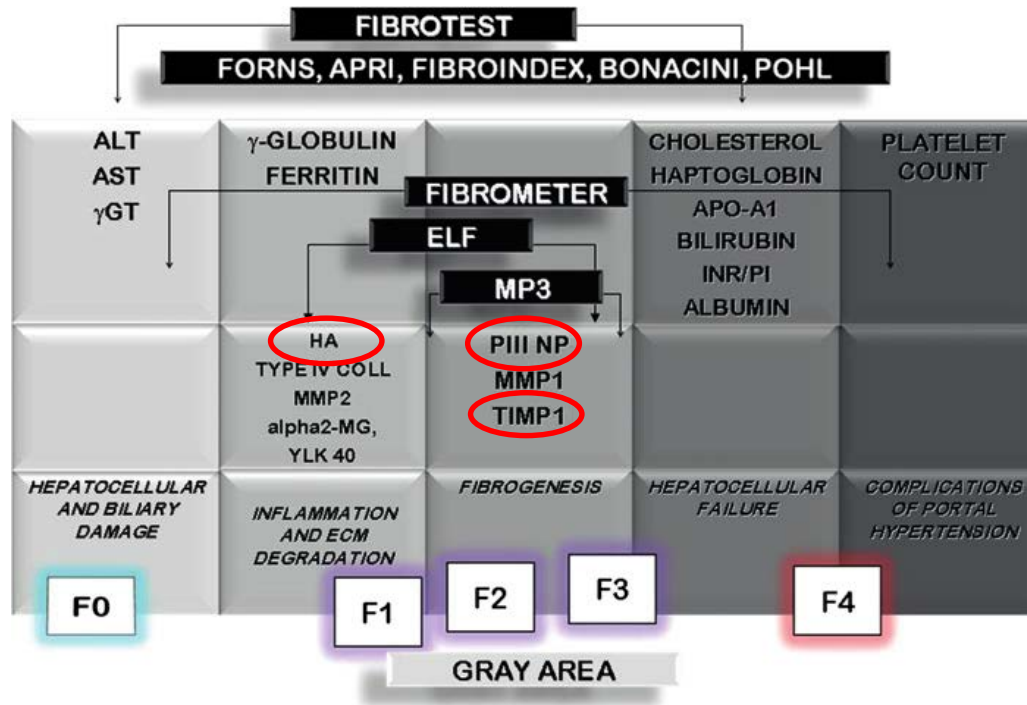


FIG. 3. Multivariate-adjusted cumulative liver disease mortality by liver fibrosis scoring system in NHANES III, United States, 1988-2011. (A) APRI. (B) FIB-4 score. (C) NFS. (D) Forns score.

Direkte fibrosemarkører




epatitis C.

Pinzani, Gut 2010, 59(9):1165-67

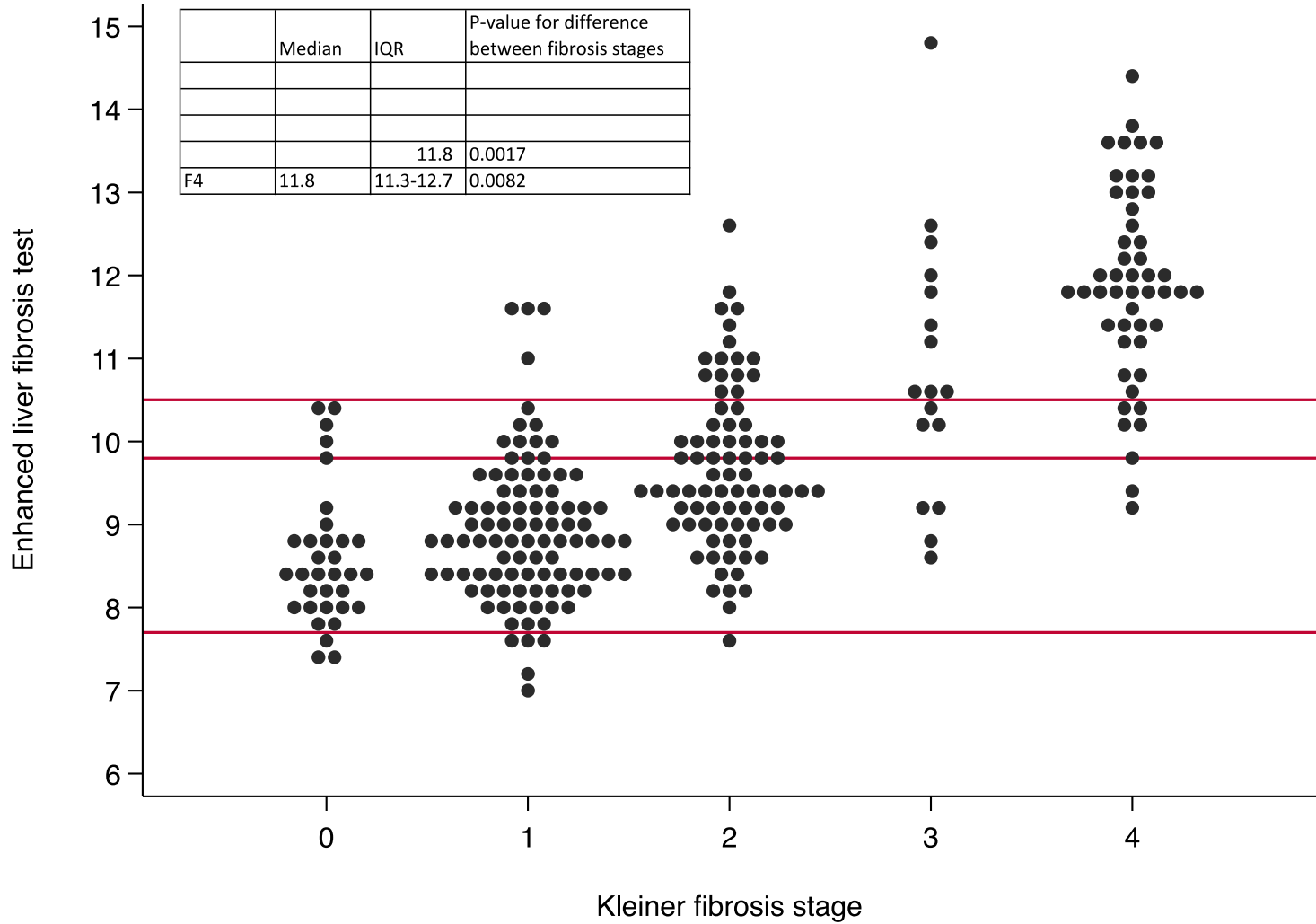
Article in Press

Accuracy of the Enhanced Liver Fibrosis Test vs Fibrotest, Elastography and Indirect Markers in Detection of Advanced Fibrosis in Patients with Alcoholic Liver Disease

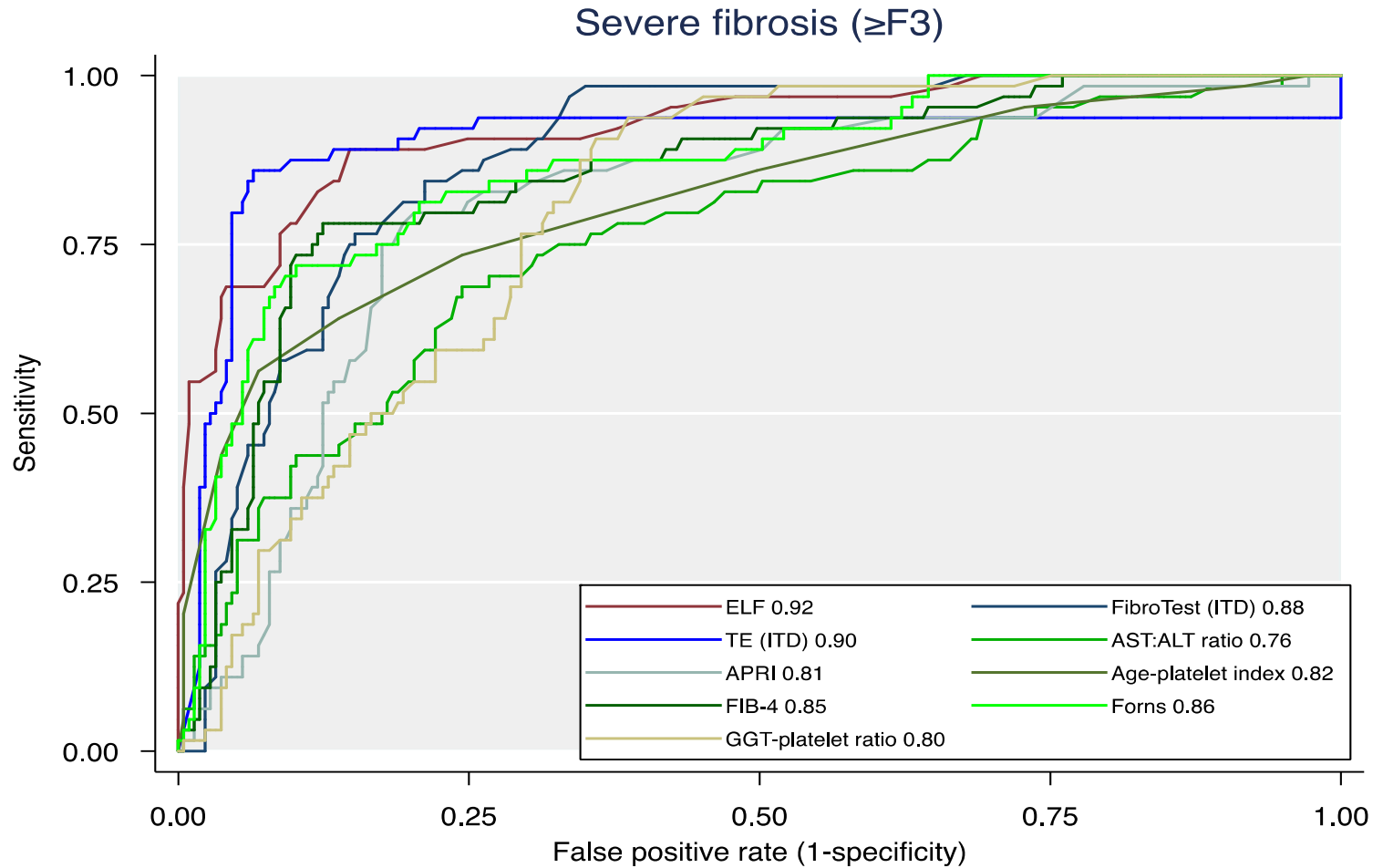
Associate professor [Maja Thiele](#)  , PhD student [Bjørn Stæhr Madsen](#), PhD student [Janne Fuglsang Hansen](#), associate professor [Sönke Detlefsen](#), head of department [Steen Antonsen](#), professor [Aleksander Krag](#)

 PlumX Metrics

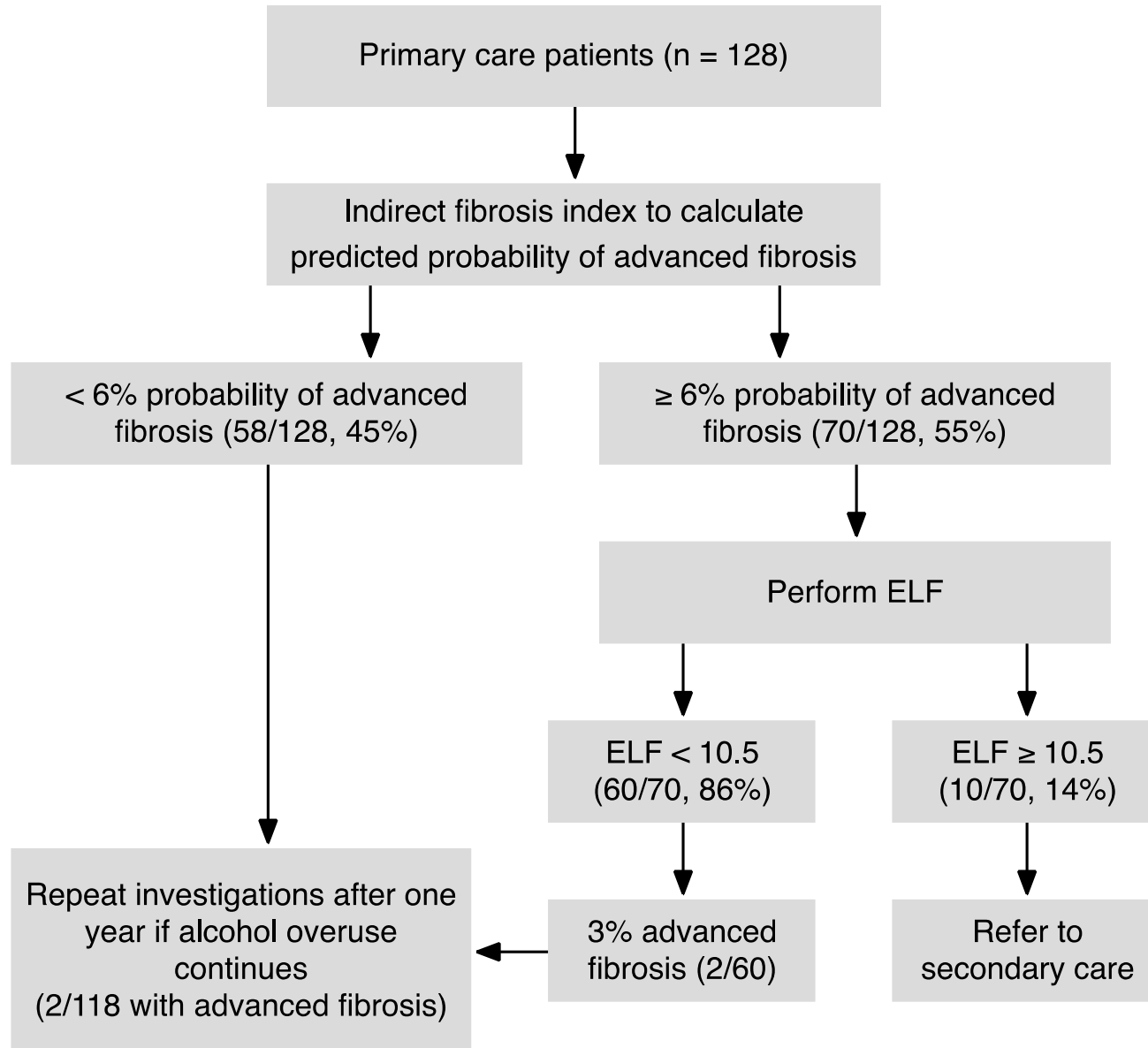
DOI: <http://dx.doi.org/10.1053/j.gastro.2018.01.005>



Thiele, Gastroenterology 2018, in press



Thiele, Gastroenterology 2018, in press



ELF og FibroScan som prognostiske markører

Predictive method	Harrell's C
elf	0.8729
te	0.9020
swe	0.8794
kleiner	0.8358
contDrink	0.5993

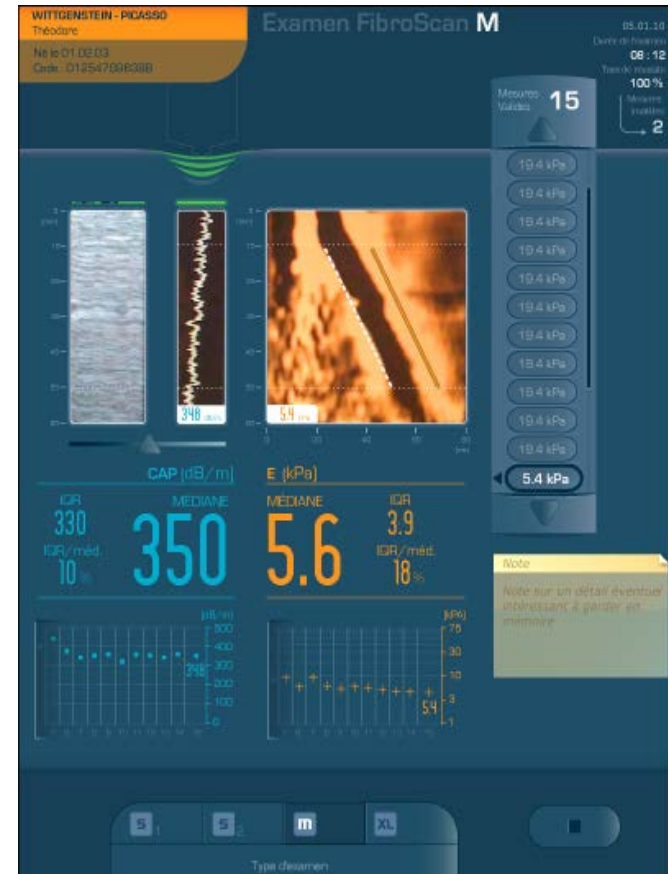
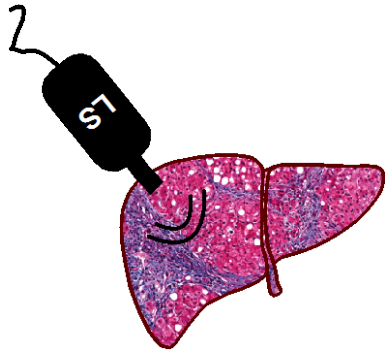
The measures of discrimination for each of the variables used in univariate predictors as calculated by Harrell's C are shown.

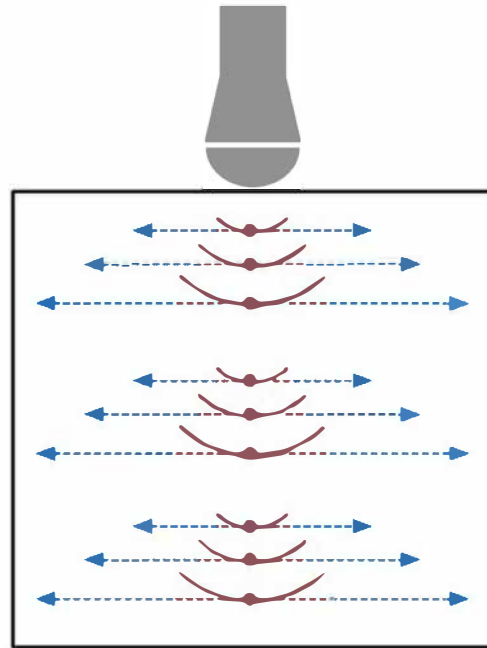
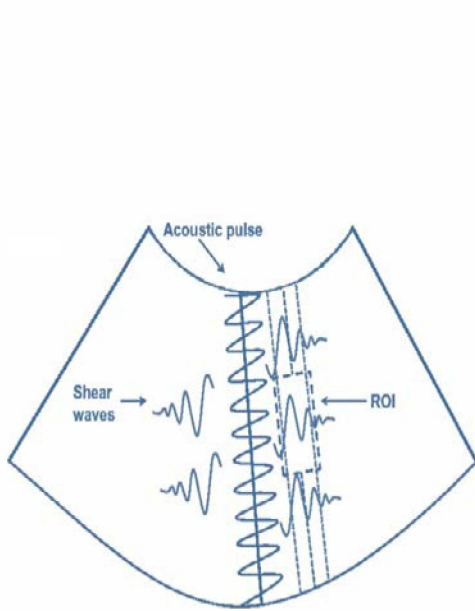
_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
elf	2.018594	.149691	9.47	0.000	1.74553	2.334376
contDrink	2.021825	.63724	2.23	0.026	1.090088	3.749952

Ditlev Rasmussen, unpublished

Elastografi = leverstivhedsmåling

Transient elastografi





Time and distance

1 second

2 second

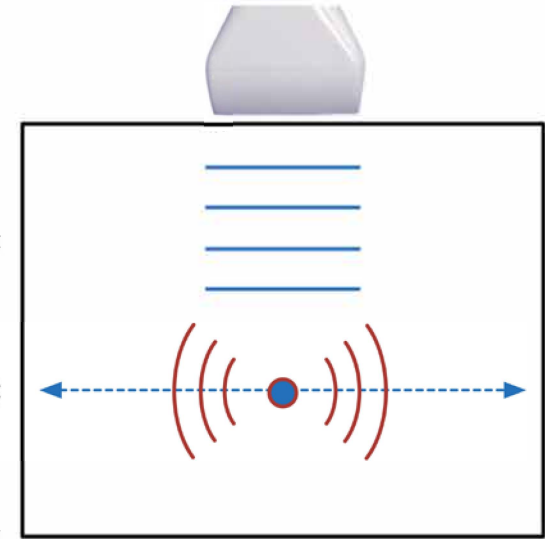
3 second

Distance

2 cm

3 cm

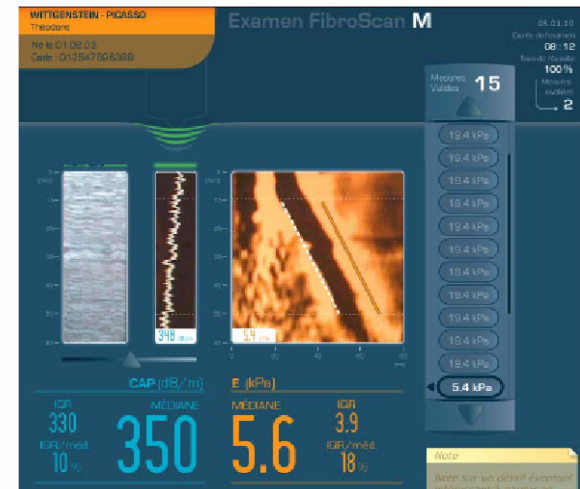
4 cm



2 cm

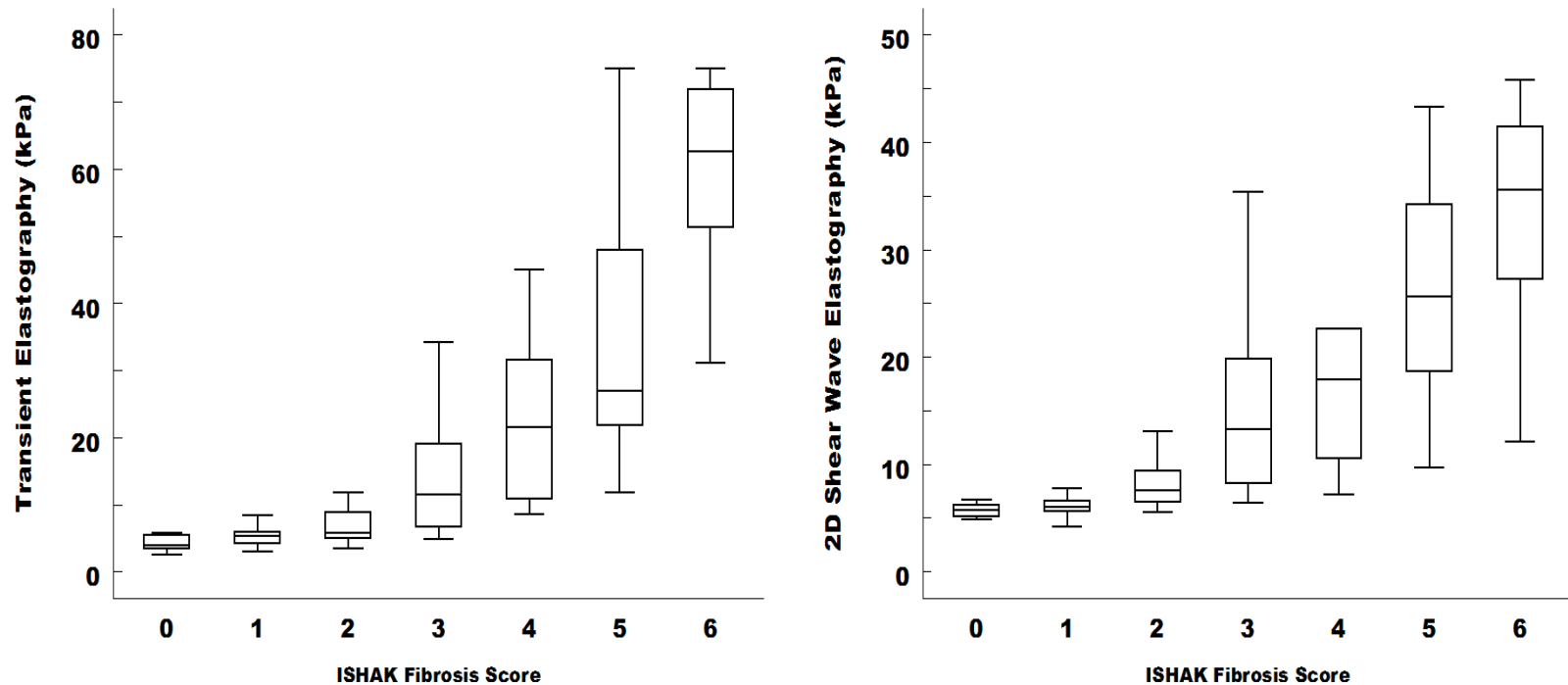
4 cm

6 cm





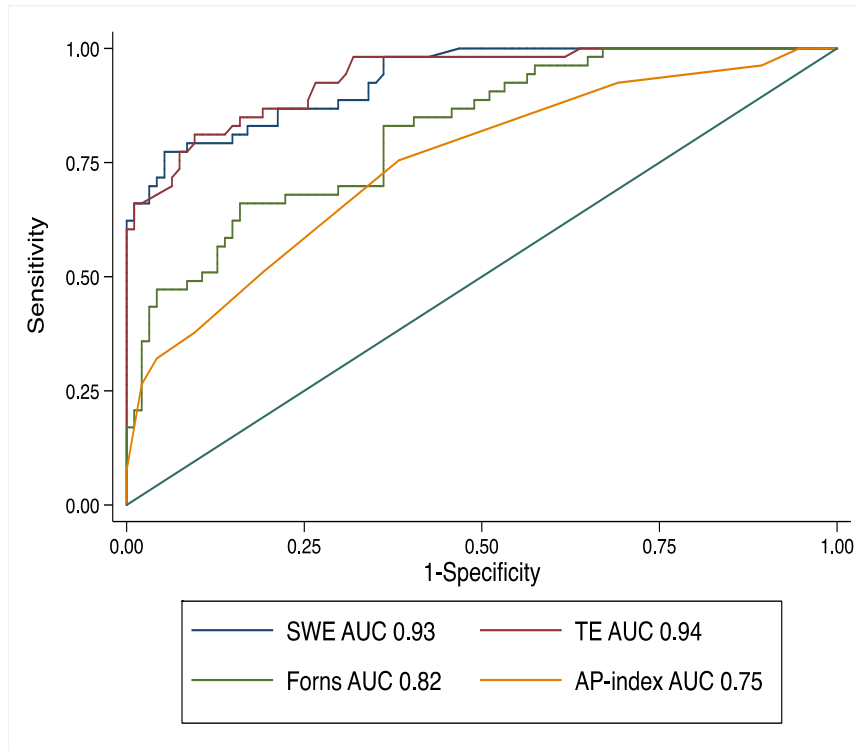
Stigende leverstivhed over fibrosegrad 0-6



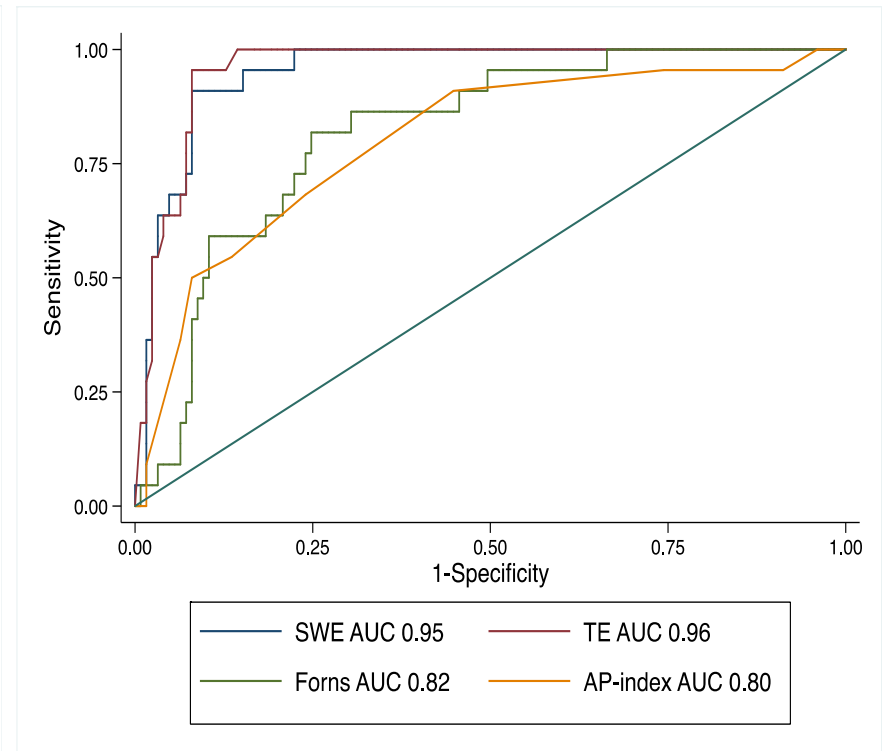
Thiele, Gastroenterology 2016, 150(1):123-133

Diagnostic accuracy of TE and 2D-SWE

Significant fibrosis



Cirrhosis



Thiele, Gastroenterology 2016, 150(1):123-133

HUSK: Falsk positive er et problem for både elastografi og blodprøvemarkører

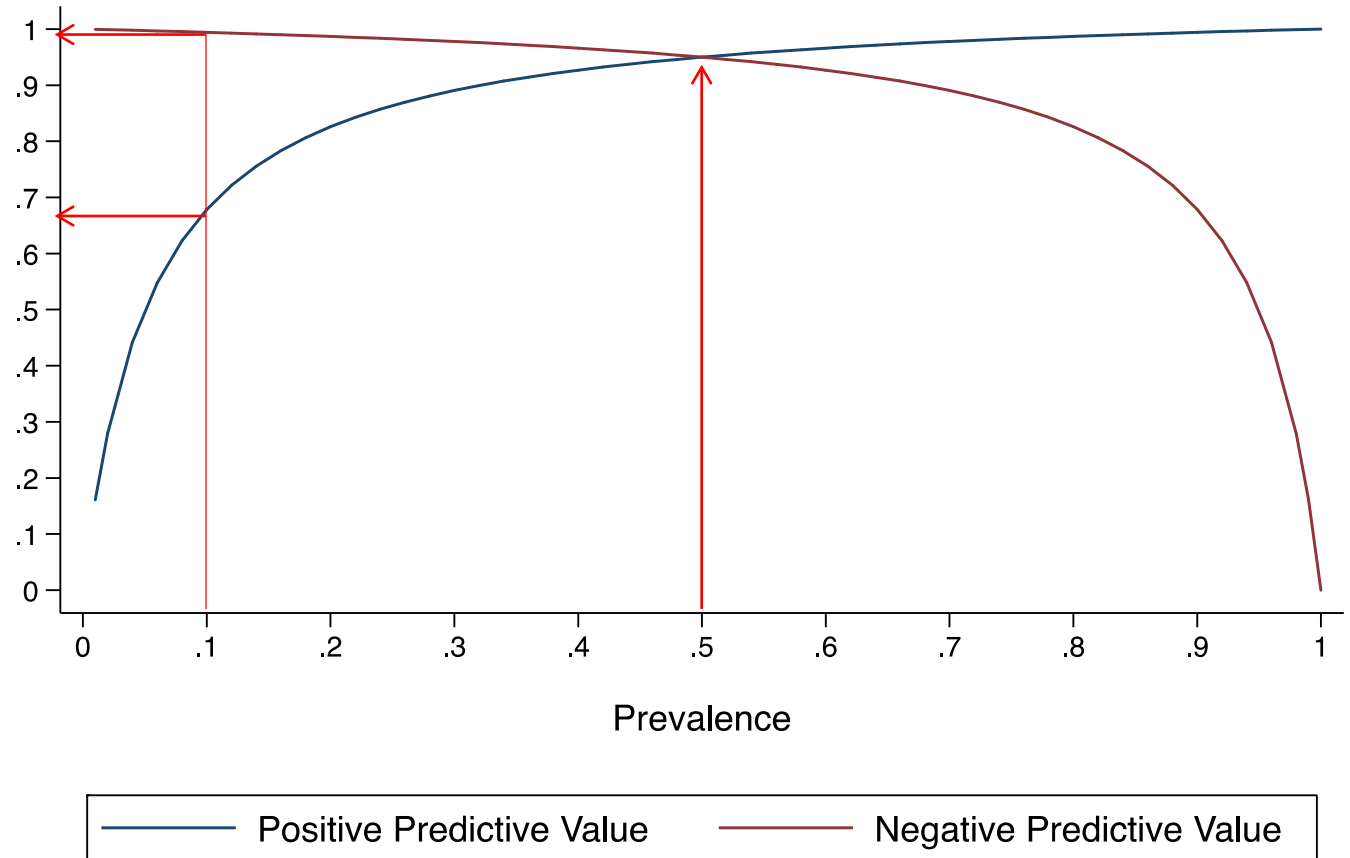
Elastography

- Inflammation
- Cholestasis
- Food
- Right heart failure
- Physical activity

ELF test

- Inflammation
- Bilirubin
- Age <30 or >60 years
- Comorbidity with other fibrogenic diseases
- Gender
- Time-of-day

Positive and negative predictive values according to disease prevalence
for a test with 95% sensitivity and specificity



Ph.D. Cup 2017 - Det Danske Hjernemesterskab

LÆSETID 3 MIN.

Maja har fundet en metode, der kan revolutionere behandlingen af skrumpelever

Hvem har svær leverfibrose?

- 57-year old female
- Excessive alcohol use for 11-20 years
- Drank 15 units (180 g) per day when at max abuse
- Still drinks
- BMI 27
- Blood pressure 174/85

- 62-year old male
- Excessive alcohol use for 21-30 years
- Drank 12 units (144 g) per day when at max abuse
- Abstinent for 1-5 years
- BMI 34
- Blood pressure 120/74

Hvem har svær fibrose?

57 year old female

62 year old male

Hvad nu?

Blodprøver

Ultralyd af leveren

57 year old female

57 årig kvinde, med 11-20 år varende alkohol overforbrug. Da forbruget var på sit højeste, drak vedkommende 15 genstande om dagen.

Drinker stadig .

BMI er 27. Blodtryk er 174/85

Blodprøvesvar		Normalværdi
Albumin	40	36-45 g/L
ALAT	21	10-70 U/L (mænd) 10-45 U/L (kvinder)
ASAT	35	15-45 U/L (mænd) 15-35 U/L (kvinder)
Basisk fosfatase	107	35-105 U/L
Bilirubin	6	5-25 µmol/L
GGT	132	10-80 U/L (mænd <40 år) 15-115 (mænd ≥40 år) 10-45 (kvinder <40 år) 10-75 (kvinder ≥40 år)
INR	0,9	0,9-1,2
Kreatinin	63	60-105 µmol/L (mænd) 45-90 µmol/L (kvinder)
Kolesterol, total	5,8	<5,0 mmol/L
Natrium	131	137-145 mmol/L
Trombocytter	302	145-350 x 10 ⁹ /L (mænd) 165-390 x 10 ⁹ /L (kvinder)

62 year old male

62 årig mand, med 21-30 år varende alkohol overforbrug. Da forbruget var på sit højeste, drak vedkommende 12 genstande om dagen.

Er nu stoppet med at drikke, og har holdt sig ædru i 1-5 år.

BMI er 34. Blodtryk er 120/74

Blodprøvesvar		Normalværdi
Albumin	45	36-45 g/L
ALAT	24	10-70 U/L (mænd) 10-45 U/L (kvinder)
ASAT	27	15-45 U/L (mænd) 15-35 U/L (kvinder)
Basisk fosfatase	45	35-105 U/L
Bilirubin	7	5-25 µmol/L
GGT	42	10-80 U/L (mænd <40 år) 15-115 (mænd ≥40 år) 10-45 (kvinder <40 år) 10-75 (kvinder ≥40 år)
INR	1,0	0,9-1,2
Kreatinin	71	60-105 µmol/L (mænd) 45-90 µmol/L (kvinder)
Kolesterol, total	5,9	<5,0 mmol/L
Natrium	138	137-145 mmol/L
Trombocytter	301	145-350 x 10 ⁹ /L (mænd) 165-390 x 10 ⁹ /L (kvinder)

57 year old female

- AST:ALT ratio =
 - 1.67
- Age-platelet index
 - 3
- APRI
 - 0.3
- FIB-4
 - 1.44
- Forns index
 - 4.6

62 year old male

- AST:ALT ratio
 - 1.13
- Age-platelet index
 - 4
- APRI
 - 0.2
- FIB-4
 - 1.14
- Forns index
 - 4.0

Hvem har svær fibrose?

57 year old female

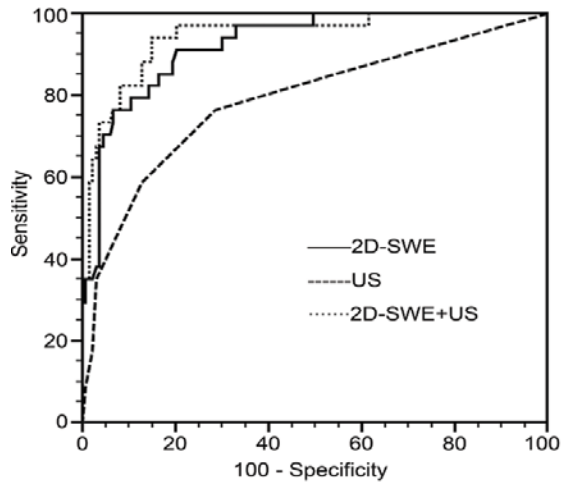
62 year old male

Hvad nu?

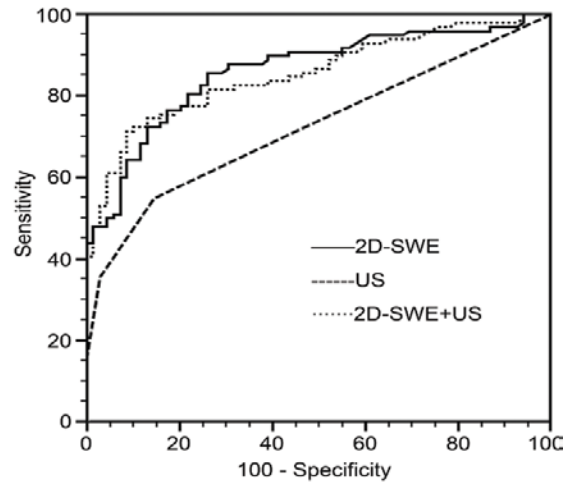
MR-Elastografi

Ultralyd af leveren

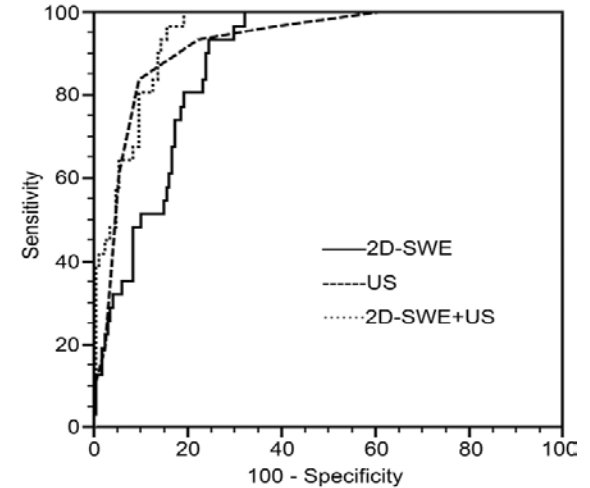
Poor diagnostic value of abdominal ultrasound in compensated disease



Significant fibrosis



Compensated cirrhosis



Decompensated cirrhosis

Zheng, Radiology 2015, 275(1):290-300

Hvad nu?

MR-Elastografi

Direkte fibrosemarkør

57 year old female

- Enhanced liver fibrosis test (ELF)
 - 8.3

62 year old male

- Enhanced liver fibrosis test (ELF)
 - 9.2

Who has advanced fibrosis?

57 year old female

62 year old male

What next?

FibroScan

2D elastografi

57 year old female

- ELF
 - 8.3
- FibroScan (TE)
 - 5.7 kPa
- 2-dimensional shear wave elastography (2D-SWE)
 - 8.2 kPa

62 year old male

- ELF
 - 9.2
- FibroScan (TE)
 - 16.2 kPa
- 2-dimensional shear wave elastography (2D-SWE)
 - 20.2 kPa

Hvem har svær fibrose?

57 year old female

62 year old male

Hvem har svær fibrose?

57 year old female
Kleiner F1

62 year old male
Kleiner F3