APASL STC Cairo 2022

Dynamics of liver fibrosis in HCV

Francesco Negro

University Hospitals of Geneva, Switzerland

Disclosures

Advisory and travel fees from Gilead, AbbVie

Speaker fee from Roche Diagnostics

Plan of the presentation

- **Before antiviral therapy**
  - **Baseline fibrosis assessment**
  - **Dynamics of fibrosis progression**
- **After treatment-induced viral clearance**
  - **Liver fibrosis regression**

The eternal PRO's and CON's of the liver biopsy

PRO's

Determines presence, extent and localization of specific lesions (e.g., rejection after LT)

Allows assessing evolution of lesions over time (e.g., after treatment)

Unsuspected comorbidities (modifies diagnosis in up to 16%)

Endpoint assessment in clinical trials

Immunohistochemistry

In situ hybridization

Allows translational research

CON's

Invasive: poor acceptance

Pain (~25%)

Hemorrhage (~2%)

Mortality (up to 0.3%)

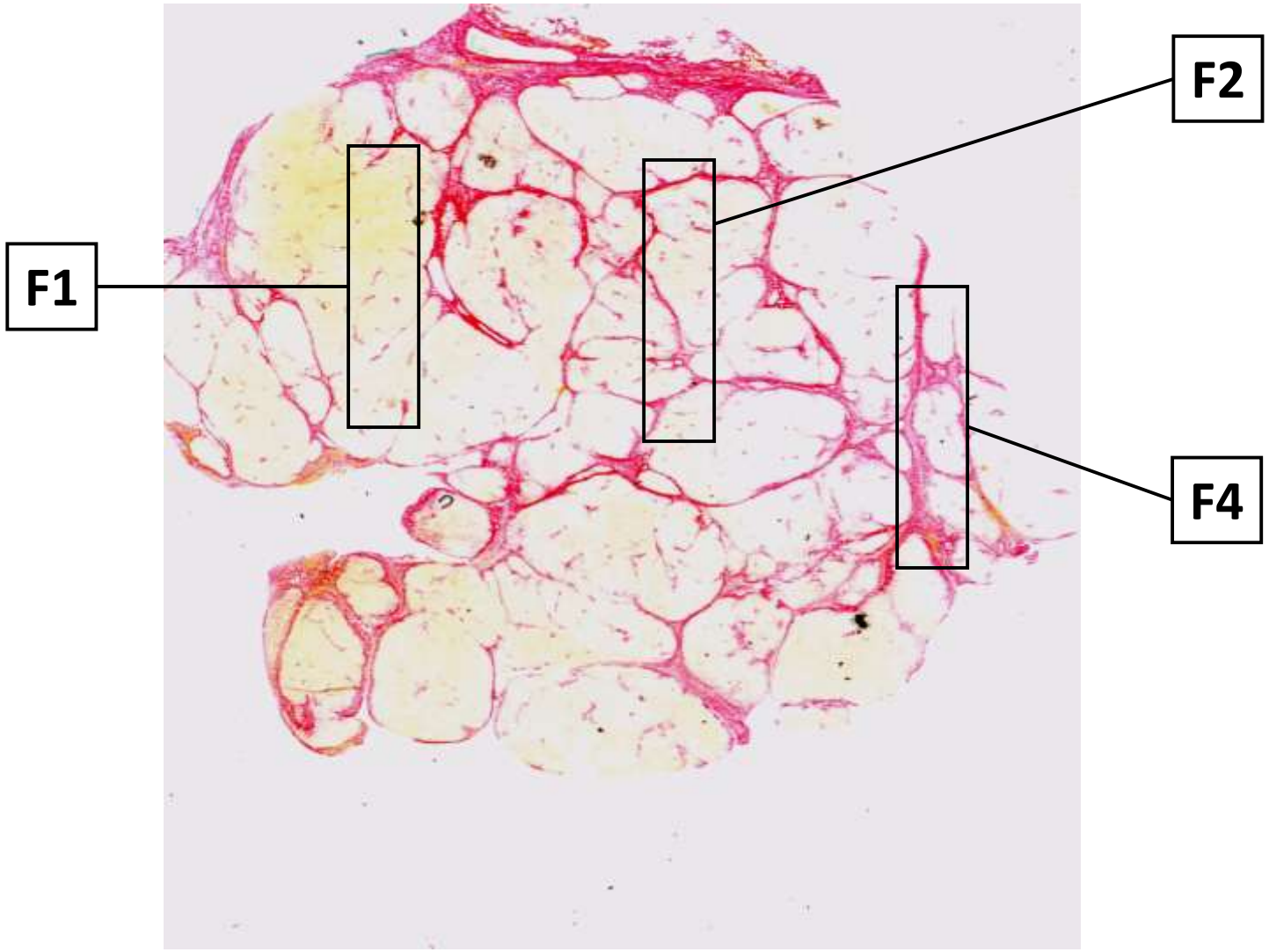
Size matters

Requires expert liver pathologist

Variability among pathologists

Sampling error

Cost



(courtesy of Pierre Bedossa)

This is a *PATTERN*

Liver Biopsy *vs.* Non Invasive Tests in Untreated Hepatitis C

The EASL Position

- Fibrosis stage before therapy *must be assessed by non-invasive methods*, including liver stiffness measurement or serum biomarkers, including APRI and FIB-4 that are inexpensive and reliable biomarker panels (A1)

- Liver biopsy should be reserved for cases where there is uncertainty or potential additional aetiologies (A1)

- Patients with cirrhosis need to be assessed for portal hypertension, including oesophageal varices

EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol 2020;73:1170-1218

Non-invasive assessment of liver disease severity

Test	Stage of fibrosis	Number of patients	Cut-off(s)	AUROC	Sensitivity	Specificity	PPV %	NPV %
FibroScan®	F3	560 HCV+	10 kPa	0.83	72%	80%	62	89
	F4	1,855 HCV+	13 kPa	0.90–0.93	72–77%	85–90%	42–56	95–98
FIB-4*	F4	2,297 HCV+	1.45 3.25	0.87 (0.83–0.92)	90% 55%	58% 92%	NA	NA
APRI**	F4	16,694 HCV+	1.0 2.0	0.84 (0.54–0.97)	77% 48%	75% 94%	NA	NA

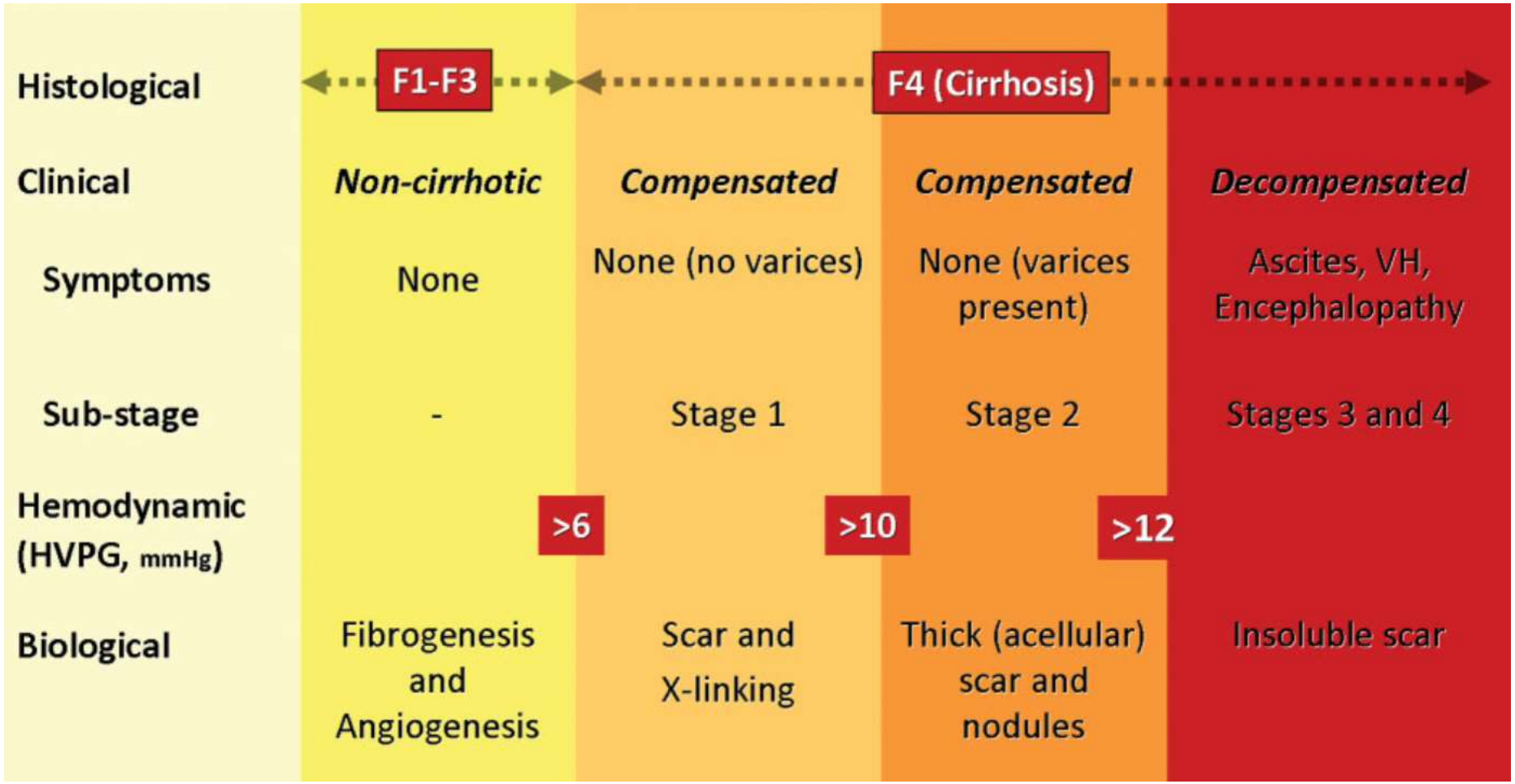
*FIB-4 = (age x AST) / (platelets x √ALT)

**APRI = [(AST/AST ULN) / platelets] x 100

EASL Recommendations on treatment of hepatitis C: final update of the series. J Hepatol 2020; 73:1170-1218

EASL™ The Home of Hepatology

Now there are many stages where before there was one!



Garcia-Tsao G, *et al.* Hepatology 2010;51:1445-9

Plan of the presentation

- **Before antiviral therapy**
  - Baseline fibrosis assessment
  - **Dynamics of fibrosis progression**
- After treatment-induced viral clearance
  - Liver fibrosis regression

Factors affecting liver fibrosis progression in hepatitis C

Factor	Author(s) (year)
Age at infection	Poynard T, *et al.* (1997, 2001), Vogt M, *et al.* (1999); Jara P, *et al.* (2003)
Sex	Poynard T, *et al.* (1997), Kenny-Walsh EE (1999), Wiese M, *et al.* (2000)
Steatosis	Hourigan LF, *et al.* (1998), Leandro G, *et al.* (2006)
Insulin resistance / T2D	Hui J, *et al.* (2003), Muzzi A, *et al.* (2005)
Excess alcohol drinking	Poynard T, *et al.* (1997), Wiley TE, *et al.* (1998), Hézode C, *et al.* (2003)
Untreated coinfection with HIV	Thein HH, *et al.* (2008), Deng LP, *et al.* (2009)
Tobacco / cannabis smoking	Pessione F, *et al.* (2001), Dev A, *et al.* (2006), Hézode C, *et al.* (2005)
HCV genotype 3	Bochud PY, *et al.* (2009)
PNPLA3	Valenti L, *et al.* (2001), Trépo E, *et al.* (2011), Patin E, *et al.* (2012)
MHC region SNPs	Urabe Y, *et al.* (2013)
MERTK, TULP1, RNF7	Patin E, *et al.* (2012)

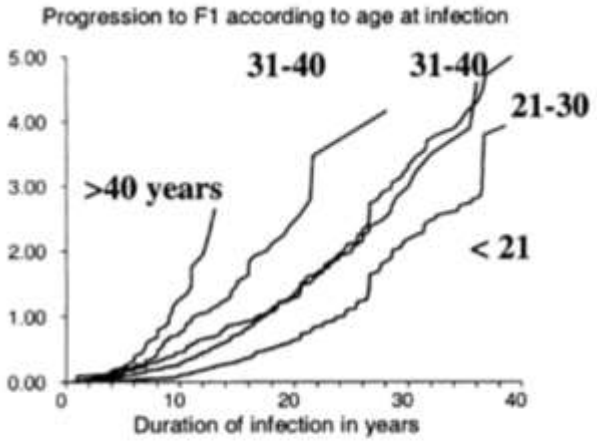
Liver fibrosis progression in chronic hepatitis C is highly variable

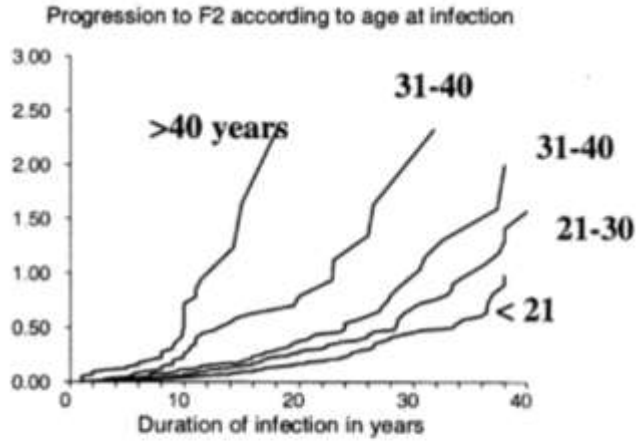
Study	Design	n	Cirrhosis incidence	Comments
Poynard T, *et al.* (1997)	Retrospective	2235	33% after a median FU of 20 years (13 yrs in men infected after 40 42 years in women infected before 40)	~31% will never develop cirrhosis after 50 yrs
Hissar SS, *et al.* (2009)	Retrospective	213	21% after 12.1 ± 8.9 years	75% with HCV-3
Tong M, *et al.* (1995)	Retrospective/ Prospective	131	51.1% after an average 20.6 years	All post-transfusion (on average, at 35 yrs)
De Ledinghen V, *et al.* (2007)	Retrospective/ Prospective	131	6.9% after 21.4 ± 6.9 years from infection	92% females (undergoing sclerotherapy)
Kenny-Walsh E (1999)	Retrospective	363	2% after 17 years	All females, mean 28-yr old at infection
Wiese M, *et al.* (2000, 2005 and 2013)	Prospective	500	0.8% after 20 years 2% after 25 years 9.3% after 35 years	All females, 16-38 yrs at infection

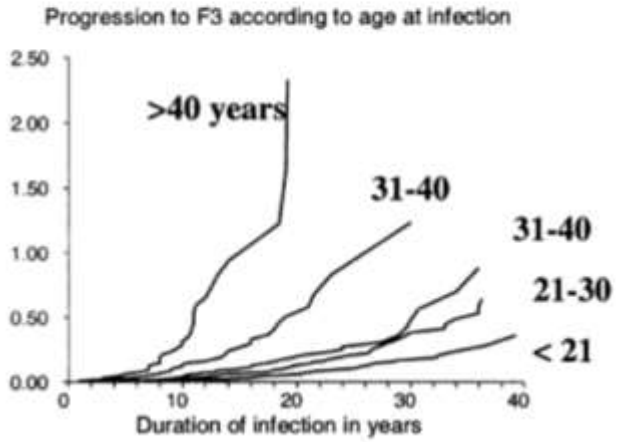
Liver fibrosis progression in untreated chronic hepatitis C with assessable date of infection (n=2313)

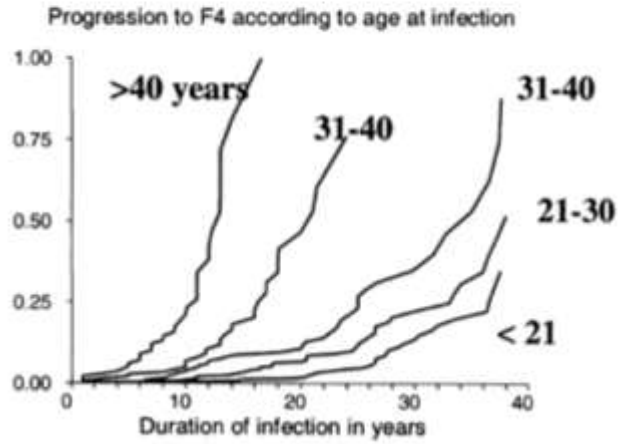
Role of age at infection

Age at infection	n
<21	754
21 – 30	851
31 – 40	348
41 – 50	211
>50	149





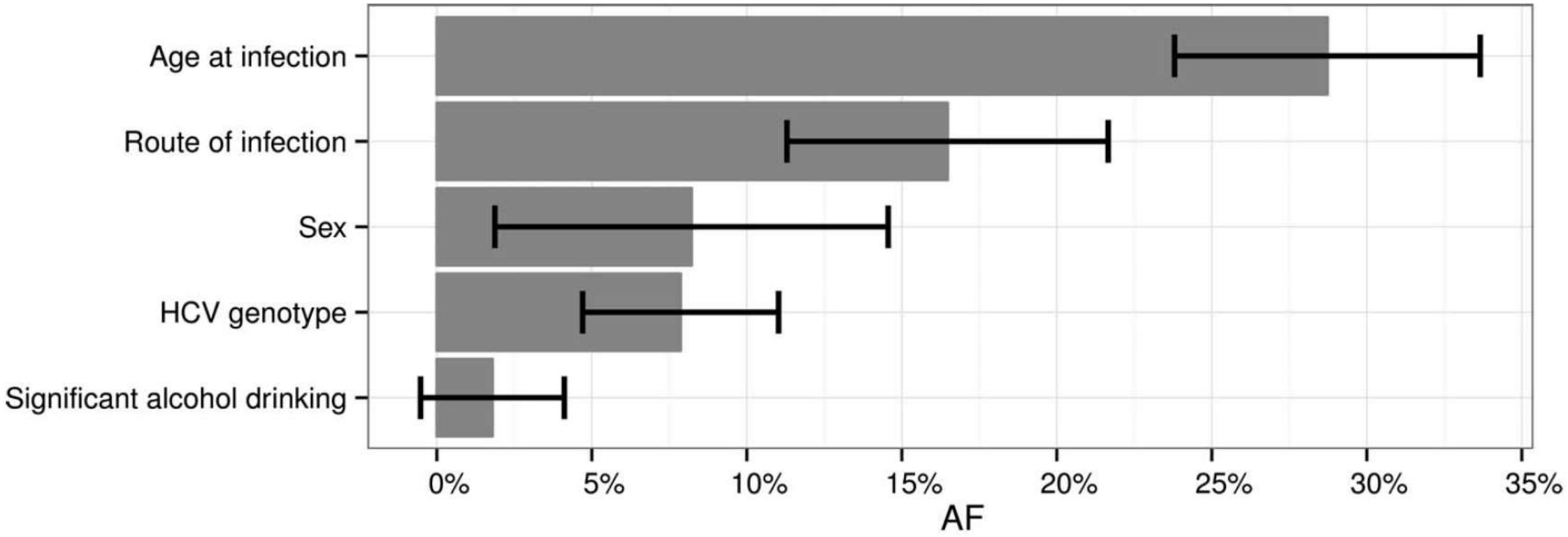




POYNARD T, *et al.* J Hepatol 2001;34:730-739

Attributable fraction of risk for fibrosis progression in chronic hepatitis C

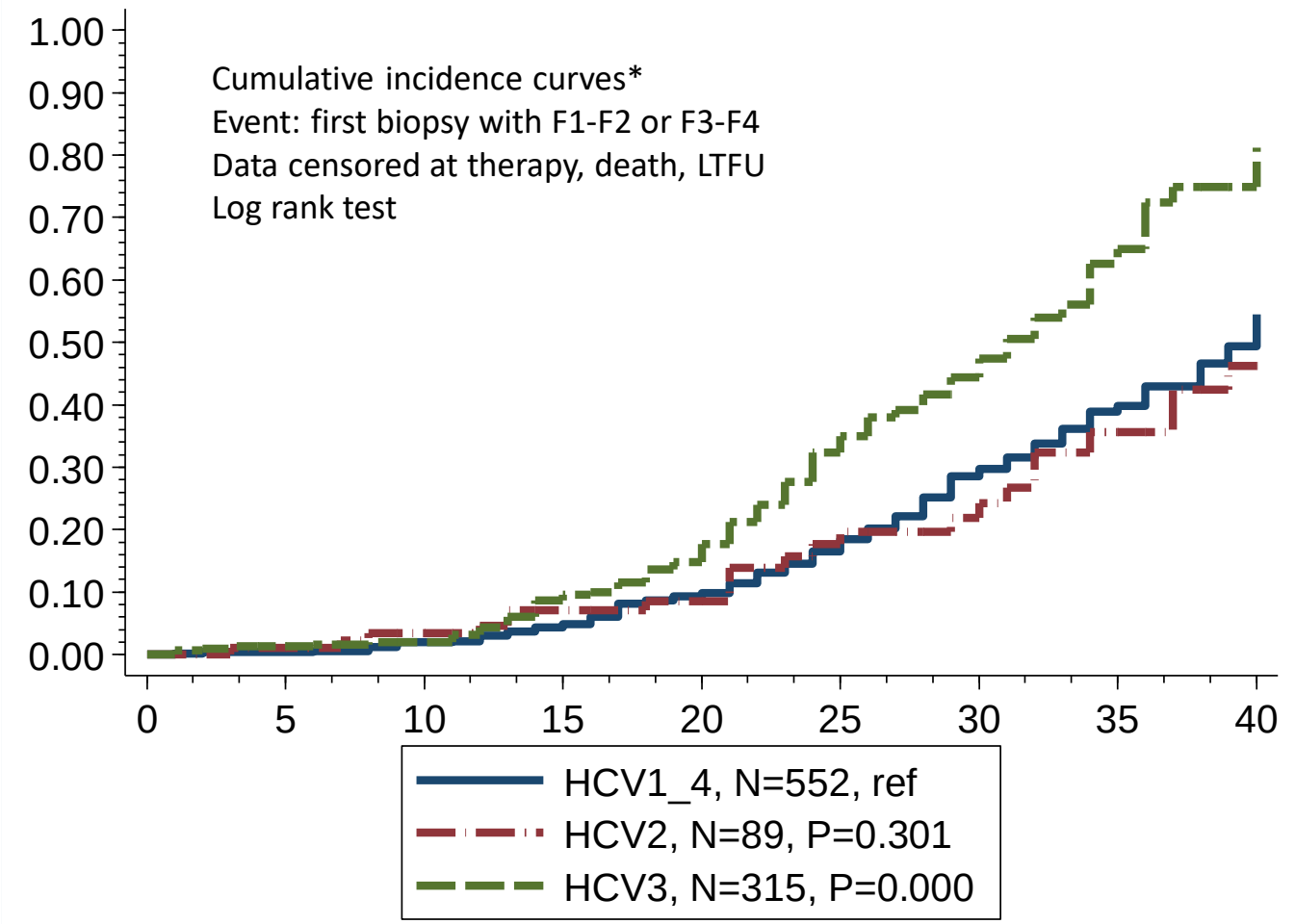
The Swiss Hepatitis C Cohort Study, whole study population, n=1461



RÜEGER S, *et al.* Gut 2015; 64:1605-15

HCV genotype 3 patients have a higher liver fibrosis progression rate

Swiss Hepatitis C Study Cohort (n=1189), with at least one liver biopsy before antiviral treatment and assessable date of infection

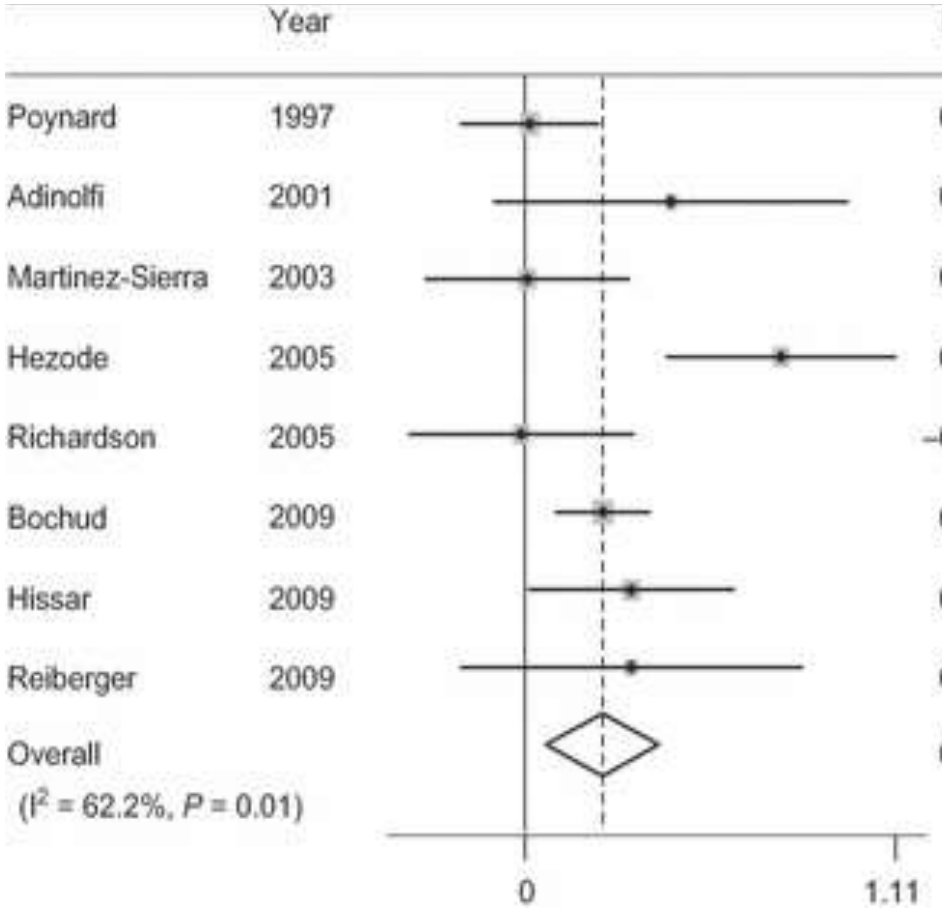


**Stage-constant and stage-specific analyses gave similar results*

BOCHUD PY, *et al.* J Hepatol 2009;51:655-666

Liver fibrosis progression rate is faster in HCV-3

Meta-analysis on HCV-3 (n=730) *vs.* other genotypes (n=1619), estimated by one biopsy



	Year	ES (95% CI)	OR (95% CI)	N genotype 3	N other genotypes	Weight (%)
Poynard	1997	0.01 (–0.19–0.22)	1.03 (0.71–1.49)	39	207	16.81
Adinolfi	2001	0.44 (–0.09–0.97)	2.21 (0.85–5.75)	25	15	6.97
Martinez-Sierra	2003	0.01 (–0.30–0.31)	1.01 (0.58–1.76)	56	132	12.98
Hezode	2005	0.77 (0.43–1.11)	4.01 (2.16–7.45)	66	201	11.66
Richardson	2005	–0.01 (–0.34–0.32)	1.36 (0.75–2.47)	88	117	11.91
Bochud	2009	0.23 (0.09–0.37)	1.51 (1.17–1.95)	327	862	19.47
Hissar	2009	0.32 (0.01–0.63)	1.78 (1.02–3.11)	105	35	12.87
Reiberger	2009	0.32 (–0.19–0.83)	1.78 (0.71–4.49)	24	50	7.33
Overall (I^2 = 62.2%, P = 0.01)		0.23 (0.06–0.40)	1.52 (1.12–2.07)	730	1619	100.00

PROBST A, *et al.* J Viral Hep 2011;18:745-59

Impact of insulin resistance/T2D in chronic hepatitis C progression

Accelerated liver fibrosis progression

- Case-control study on 121 chronic hepatitis C patients with F0-F1, matched to uninfected controls by sex, BMI, waist-to-hip ratio
- By MV, the HOMA-IR score (but not steatosis) was independently associated with fibrosis stage (P<0.001) and progression rate (P=0.03)

HUI J, *et al.* Gastroenterology 2003;125:1695-704

Increased risk of HCC

- 541 chronic hepatitis C patients (Ishak 4-6, 85 with diabetes), median FU 4.0 years
- Diabetes: independent predictor of HCC in patients with Ishak 6 (HR 3.28, 95% CI 1.35-7.97, P=.009)

VELDT C, *et al.* Hepatology 2008;47:1856-62

Increased risk of cirrhosis complications

- Single center retrospective study (n=348)
- By MV, increased risk of bacterial complications (HR 2.098, 95% CI 1.227 – 3.589, P=0.007)

ELKRIEF L, *et al.* Hepatology 2014;60:823-31

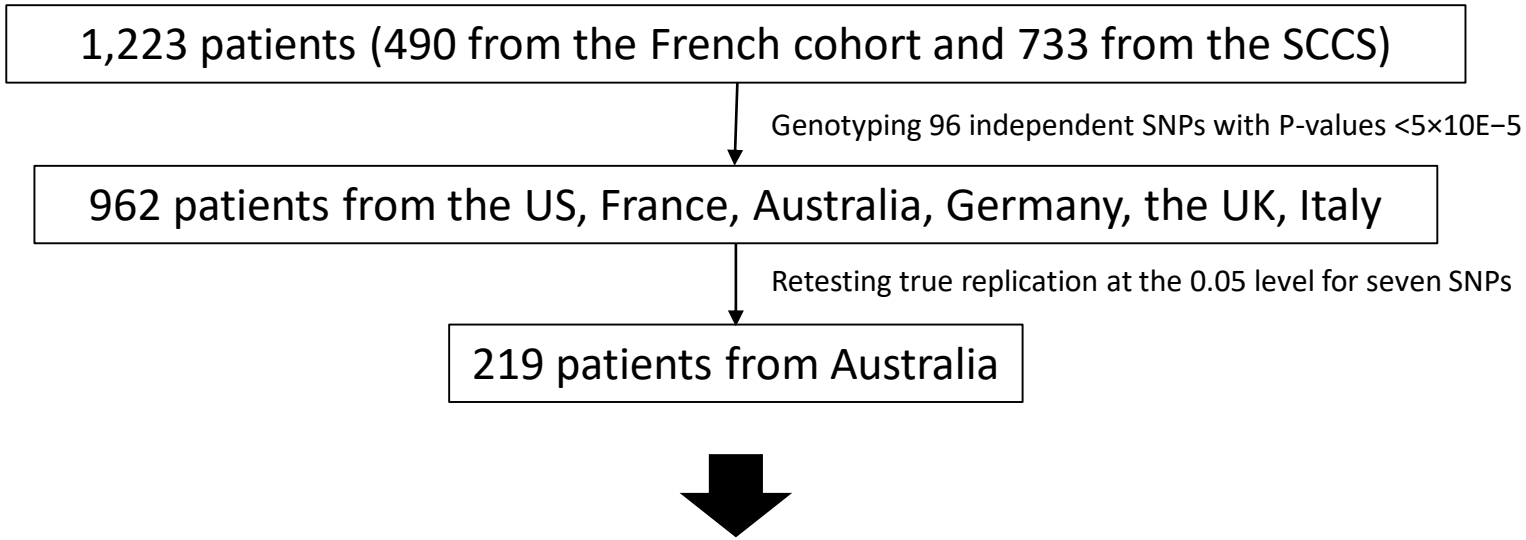
Increased risk of cirrhosis decompensation and liver-related death

- Multicenter US HALT-C Trial (n=737): HOMA-IR score (by quartile, HR 1.25 (95% CI 1.08-1.45)

EVERHART JE, *et al.* Gastroenterology 2009;137:549-57

Host genetic variants associated with progression of liver fibrosis in HCV

A genome-wide association study



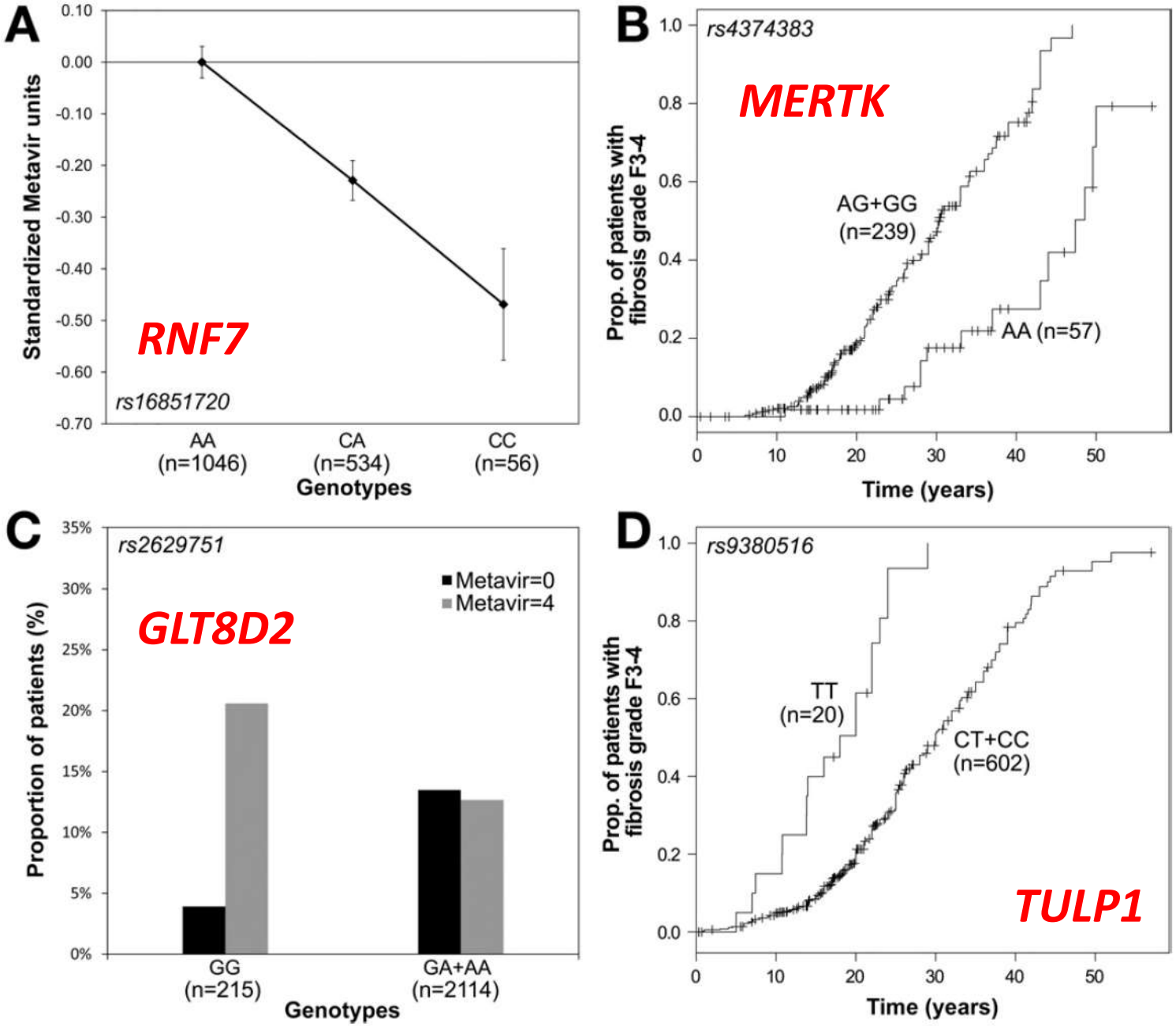
rs16851720, P=8.9×10E−9 (intronic SNP in *RNF7*)

rs4374383, P=1.1×10E−9 (intronic SNP in *MERTK*)

rs2629751, P=1.4×10E−7 (intronic SNP in *GLT8D2*)

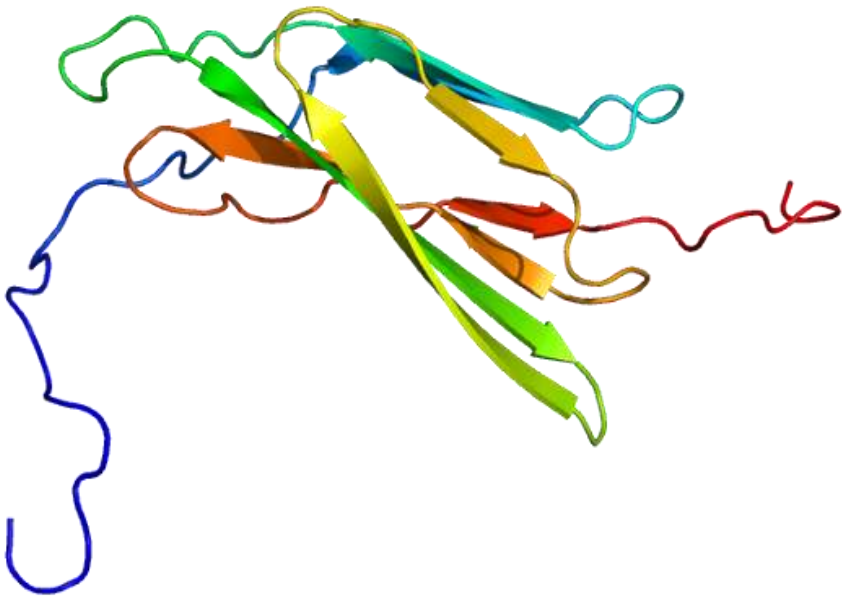
rs9380516, P=5.4×10E−7 (21 kb downstream from *TULP1*)

PATIN E, *et al.* Gastroenterology 2012;143:1244-52



PATIN E, *et al.* Gastroenterology 2012;143:1244-52

MERTK (Myeloid Epithelial Reproductive Tyrosine Kinase)

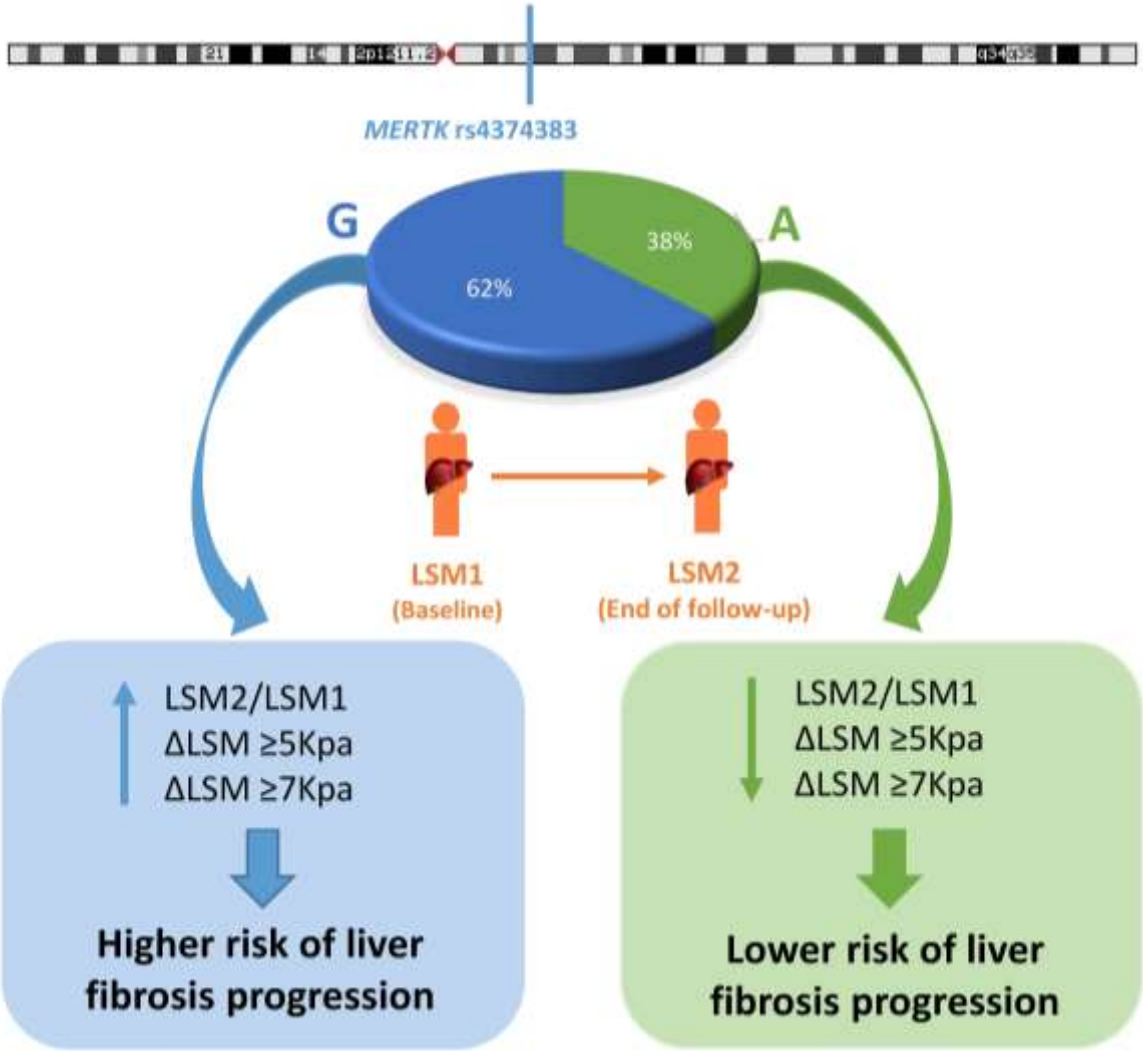


- Transmembrane receptor highly expressed in liver resident macrophages (Kupffer cells)
- Involved in phagocytosis of apoptotic cells, cell survival, thrombosis
- Mutations are responsible for the autosomal recessive retinitis pigmentosa *via* disruption of the retinal pigment epithelium phagocytosis
- Activation *via* interaction with its ligand Gas6 leads to TGFβ1 overexpression and hepatic stellate cell activation
- It is inactivated by ADAM17 protease-mediated cleavage

Gal A, *et al.* Nat Gen 2000;26:270-1; Nagata K, *et al.* J Biol Chem 1996;271:30022-27
Sather S, *et al.* Blood 2007; 109:1026-33; Thorp E, *et al.* J Biol Chem 2011; 286:33335-44; Cai B, *et al.* Cell Metab 2020;31:406-421

MERTK rs4374383 G carriers are at risk of liver fibrosis progression in hepatitis C

- Retrospective study
- 208 non-cirrhotic chronic hepatitis C
- 85% genotype 1
- Liver stiffness measurements (LSM) across a median FU of 46.6 months
- 26 patients developed cirrhosis



JIMENEZ-SOUSA MA, *et al.* J Clin Med 2018;7:473

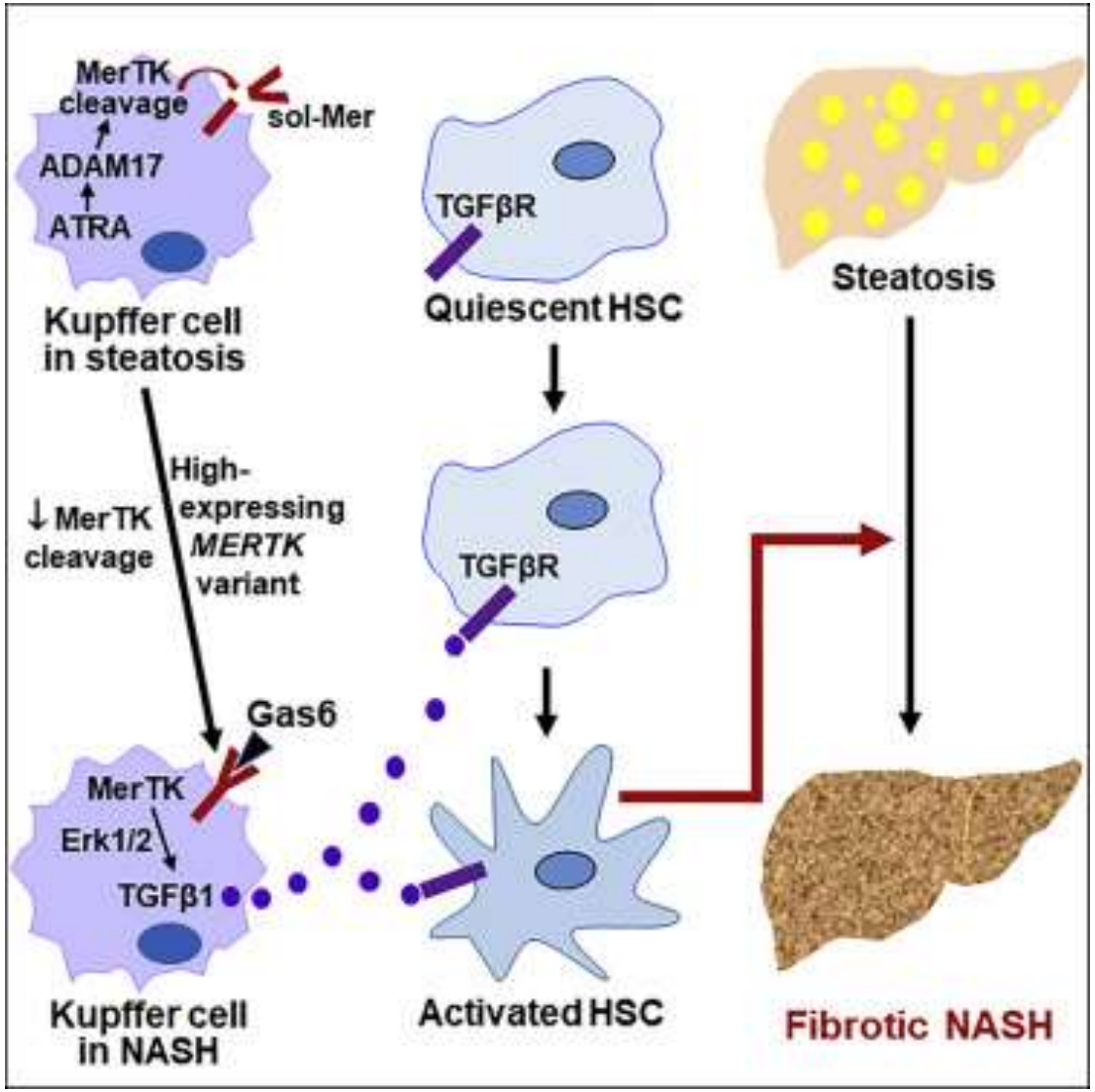
The *rs4374383* AA genotype is associated with lower levels of intrahepatic MERTK and lower prevalence of fibrosis in NAFLD

- 533 consecutive, non-obese patients undergoing diagnostic evaluation for NAFLD
- Clinically significant fibrosis (F2-F4) was observed in 19% of patients with *MERTK* AA compared to 30% in those with *MERTK* GG/GA (OR 0.43, 95% CI 0.21–0.88, p=.02)

Variable	Significant fibrosis		
	Unadjusted model[&]	Adjusted model 2*	Adjusted model 3[§]
	OR (95% CI) *p* value		
Mean age, yr	1.03 (1.02-1.05) <0.001	1.05 (1.02-1.07) <0.001	1.04 (1.02-1.06) <0.001
ALT, IU/L	1.01 (1.00-1.01) <0.001	1.01 (1.00-1.01) 0.001	1.00 (1.00-1.01) 0.003
Type 2 diabetes	3.02 (1.92-4.93) <0.001	2.03 (1.16-3.54) 0.01	1.91 (1.06-3.45) 0.03
NASH	10.7 (6.78-17.0) <0.001	-	7.19 (3.81-13.5) <0.001
MERTK GG/GA *vs.* AA	0.54 (0.30-0.99) 0.04	0.40 (0.20-0.81) 0.01	0.43 (0.21-0.88) 0.02
PNPLA3 CC *vs.* CG *vs.* GG	1.29 (0.99-2.69) 0.05	1.05 (0.77-1.43) 0.75	1.01 (0.73-1.40) 0.90
TM6SF2 CC *vs.* CT/TT	1.23 (0.72-2.08) 0.44	1.26 (0.69-2.32) 0.44	1.28 (0.67-2.43) 0.44
Southern Italian cohort	5.58 (3.69-8.46) <0.001	5.07 (3.19-8.08) <0.001	1.41 (0.75-2.66) 0.27

PETTA S, *et al.* J Hepatol 2016;64.682-690

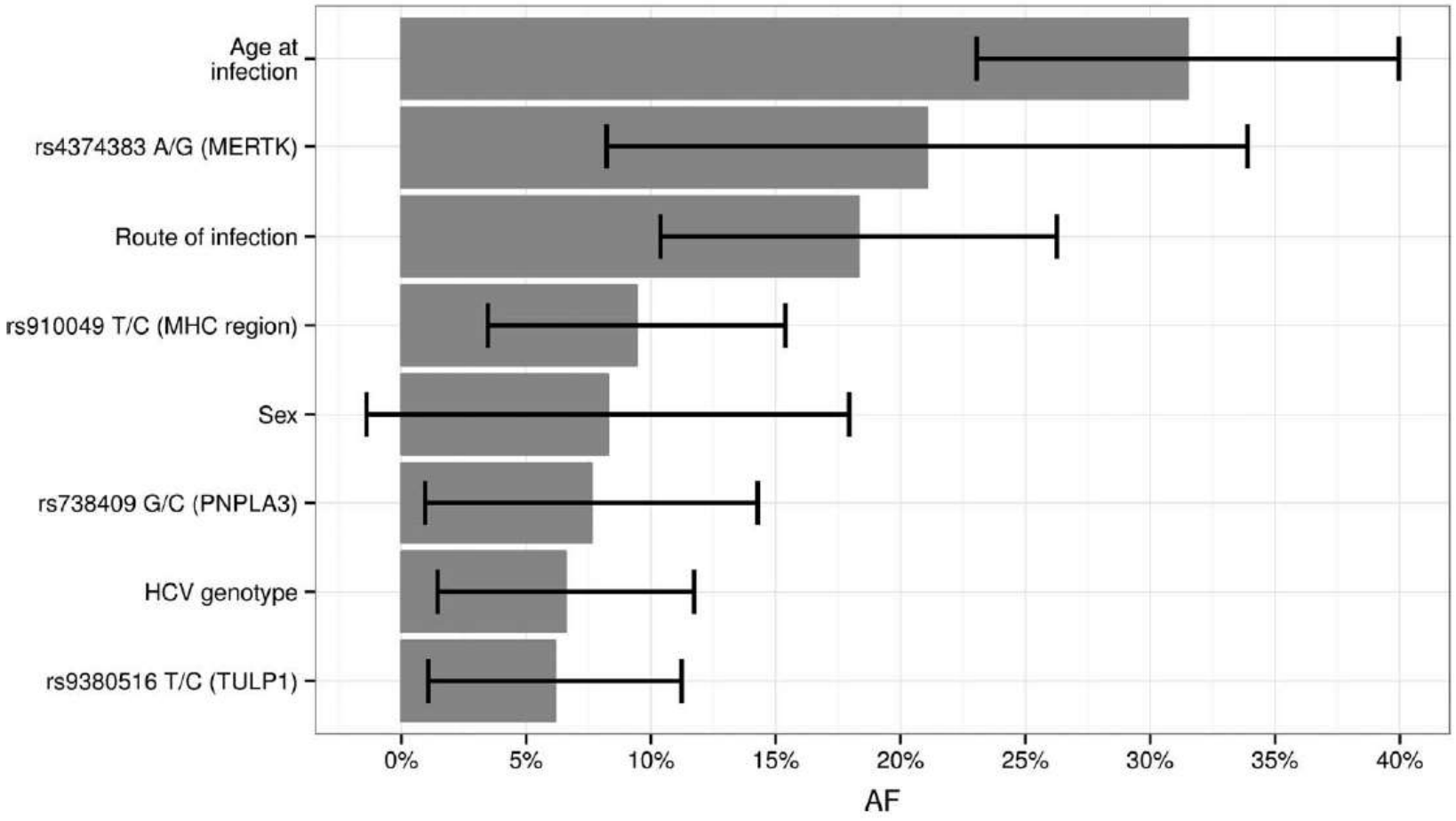
Macrophage MerTK Promotes Liver Fibrosis in Nonalcoholic Steatohepatitis in Mice



Cai B, *et al.* Cell Metab 2020;31:406-421

Attributable fraction of risk for fibrosis progression in chronic hepatitis C

The Swiss Hepatitis C Cohort Study, subgroup with host SNPs from GWA, n=590



RÜEGER S, *et al.* Gut 2015; 64:1605-15

Attributable fraction of risk for liver fibrosis progression in chronic hepatitis

A meta-analysis

(Swiss Cohort, n=590; French cohort, n=403; FR-US cohort, n=470; Sydney Cohort, n=219)

	AF (95% CI)	P
Sex	**11.8% (6.7% - 16.8%)**	**< 0.0001**
Age at infection	**34.8% (29.2% - 40.5%)**	**< 0.0001**
HCV genotype 3 vs. non-3	**4.2% (1.5% - 6.9%)**	**0.002**
rs9380516 (TULP1)	**2.6% (-0.8% - 6.0%)**	0.13
rs738409 (PNPLA3)	**6.8% (2.2% - 11.3%)**	**0.004**
rs910049 **(MHC region)**	**5.9% (1.8% - 10.1%)**	**0.005**
rs4374383 (MERTK)	**13.3% (5.6% - 20.9%)**	**0.0007**

Liver fibrosis progression in chronic hepatitis C is largely due to *unmodifiable* factors

RÜEGER S, *et al.* Gut 2015;64:1605-15

Plan of the presentation

- Before antiviral therapy
  - Baseline fibrosis assessment
  - Dynamics of fibrosis progression
- **After treatment-induced viral clearance**
  - **Liver fibrosis regression**

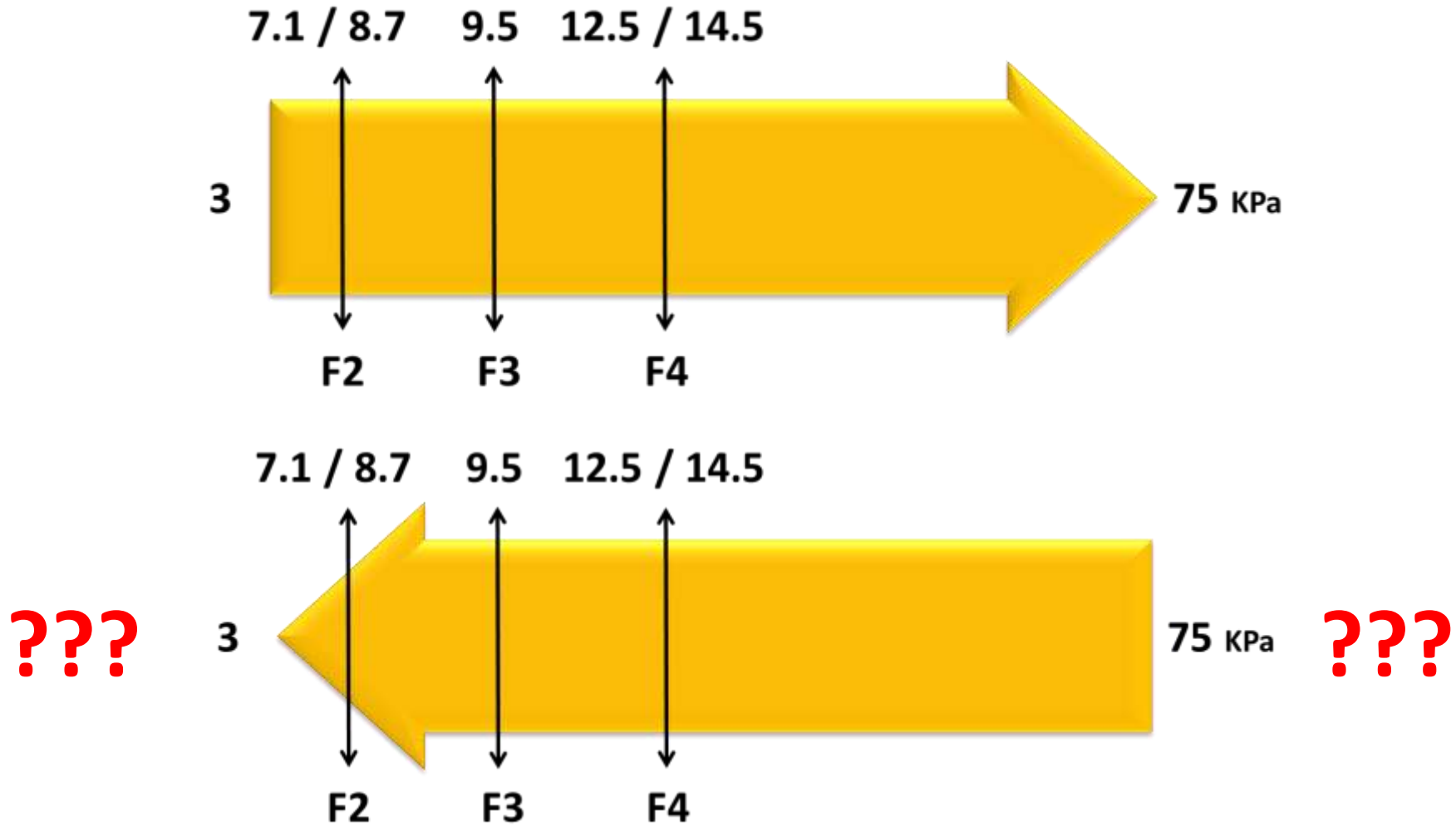
Liver Fibrosis Regression in HCV-Related Cirrhosis After Sustained Virologic Response

D'AMBROSIO R, *et al.* Hepatology 2012;56:532-43

Assessing Liver Fibrosis in hepatitis C by non-invasive tests after SVR
A Cautionary Note

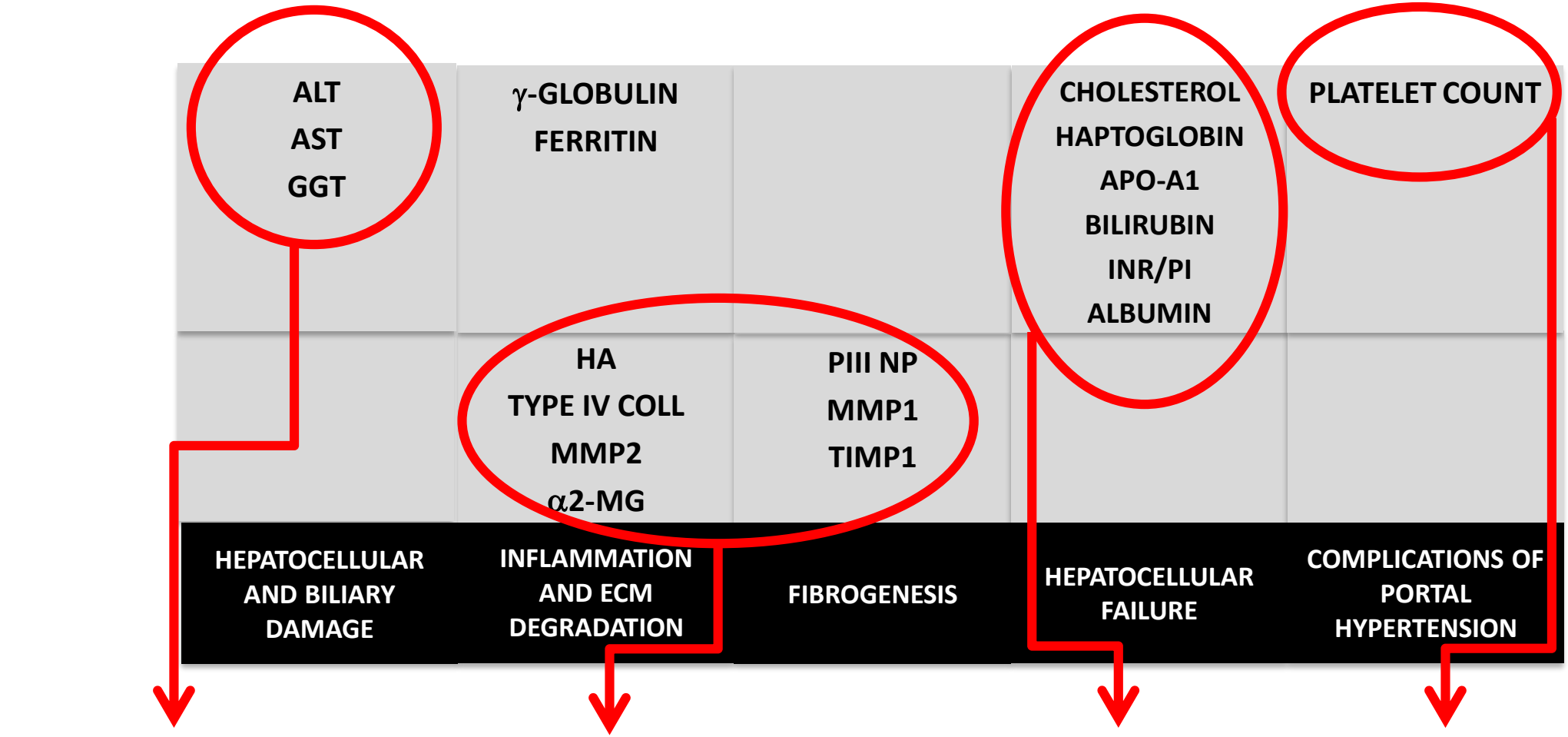
- **Viral eradication is reached very rapidly (2-3 months), while fibrosis regression is slow and stage-dependent**
- **A rapid decrease of some non-invasive tests (e.g., liver stiffness) may reflect the initial decrease of inflammation, rather than fibrosis**
- **Impact of persisting comorbidities affecting the liver (excess alcohol drinking, insulin resistance/diabetes)**

Transient Elastography is reliable to assess fibrosis progression in untreated patients, but is it the same on the way back, i.e., after viral clearance?



(courtesy of Massimo Pinzani)

Fibrosis Serum Markers Following HCV Eradication:
Transient elastography may perform better than common serum marklers



(courtesy of Massimo Pinzani)

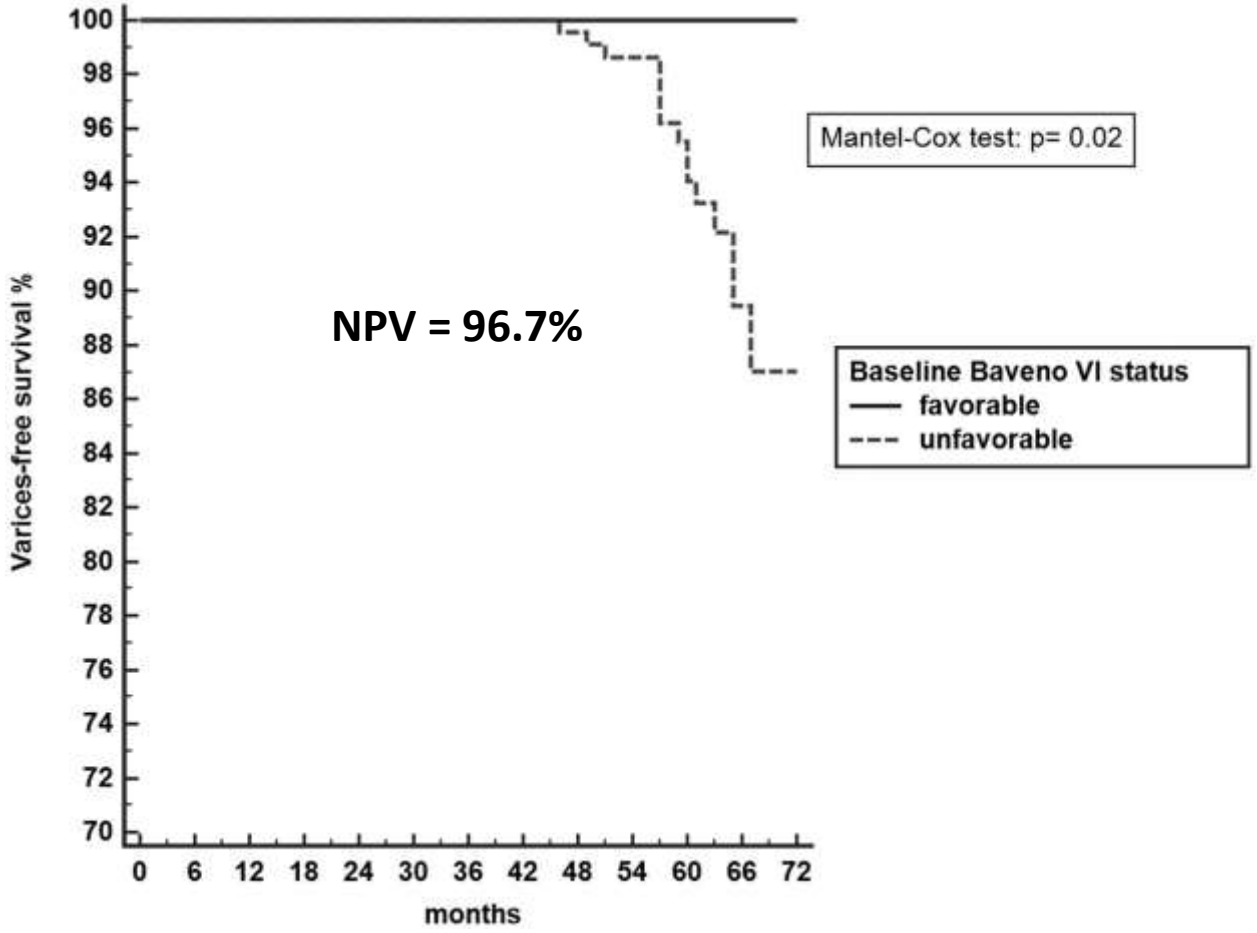
Factors Affecting the Dynamics of Fibrosis Regression in Cirrhosis as Measured by Transient Elastography

Histopathology	Dynamics	Diagnostic Value
Biochemistry of cirrhotic tissue: extensive cross-linking, elastin content	No changes	Low
Necro-inflammation/swelling	Rapid changes	Low
Established fibrosis with limited neo-angiogenesis	Slow changes	Acceptable
Established fibrosis with extensive neo-angiogenesis	Very slow changes	Low
Cholestasis	Very slow changes	Low

Pinzani M, Seminars Liver Dis 2015

Unfavorable Baveno VI status* before DAA therapy predicts *de novo* appearance of oesophageal varices in patients with HCV-related cirrhosis and SVR

Single-center prospective cohort, n=427, Child A-B



*Platelets <150 G/L, TE >20 kPa

Ciancio S, *et al.* Liver Int 2022;42:1121-1131

Dynamic assessment of GES score to predict HCC after DAA-associated SVR in hepatitis C

Variable	Score
Sex	
Female	0
Male	3.5
Age	
≤54 years	0
>54 years	1
Fibrosis stage	
F0-2	0
F3	1.5
F4	3
Albumin	
≥ 3.8 g/dL	0
<3.8 g/dL	2
Alpha-fetoprotein	
≤20 ng/mL	0
> 20 ng/mL	3
Total	0–12.5

Low = ≤ 6
Intermediate = > 6 – 7.5
High = > 7.5

Pre-treatment risk score	Post-treatment risk score	Non-HCC	HCC	5-year cumulative incidence (95% CI)
Low (n=1857)	Low (n=1470)	1436	34	1.21 (0.85-1.67)
	Intermediate (n=338)	323	15	2.33 (1.31-3.85)
	High (n=49)	39	10	10.53 (5.35-18.76)
Intermediate (n=719)	Low (n=190)	181	9	2.38 (1.16-.37)
	Intermediate (n=419)	390	29	3.16 (2.16-4.48)
	High (n=110)	77	33	10.91 (7.64-15.15)
High (n=499)	Low (n=104)	101	3	1.51 (0.38-4.11)
	Intermediate (n=187)	163	24	6.18 (4.05-9.05)
	High (n=208)	153	55	11.31 (8.60-14.61)

Shiha G, *et al.* Liver Int 2021;41:2768-2776

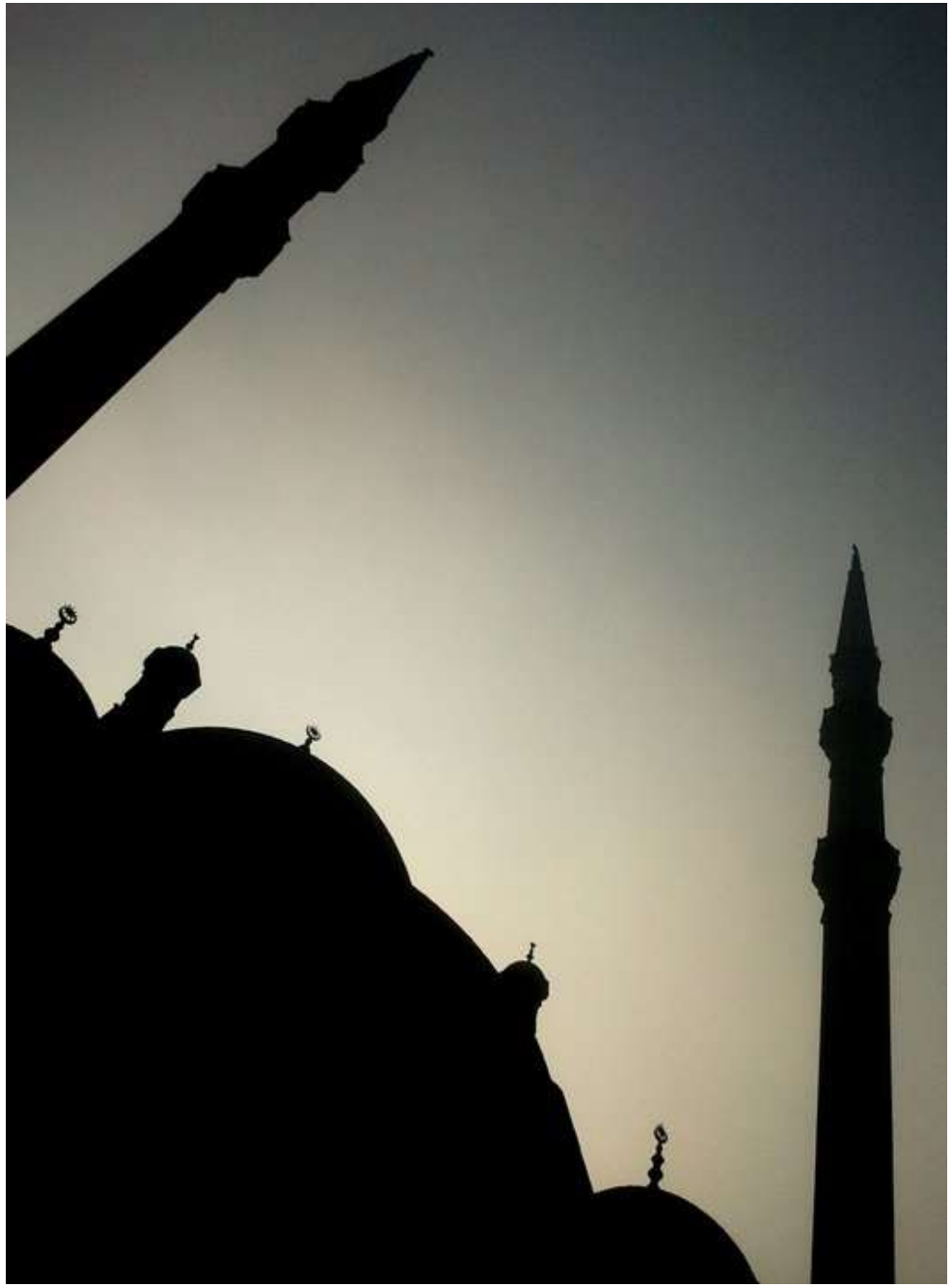
Assessing liver fibrosis in hepatitis C: take-home messages

Before antiviral therapy, **non-invasive tests are favored for staging patients and establishing management priorities**

Liver fibrosis progression in untreated hepatitis C depends largely by *unmodifiable cofactors*

After viral clearance induced by antivirals, **fibrosis (and liver disease) regression depends on the severity of neo-angiogenesis and biochemical changes of fibrous septa**

Accurate prognostic assessment **cannot rely only on fibrosis markers but may require additional parameters, especially in patients with advanced liver fibrosis, both before and after antiviral therapy**



شكرا