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**Healthy Liver
Cirrhosis**

**Storia naturale dell'epatite HCV-
correlata in assenza di terapia**

Paestum – 13-15 Maggio 2004



The Natural History of Hepatitis C Infection

Difficulties

- ❖ usually asymptomatic onset
- ❖ usually asymptomatic course
- ❖ long disease duration 30-40 yrs
- ❖ often presence of co-factors

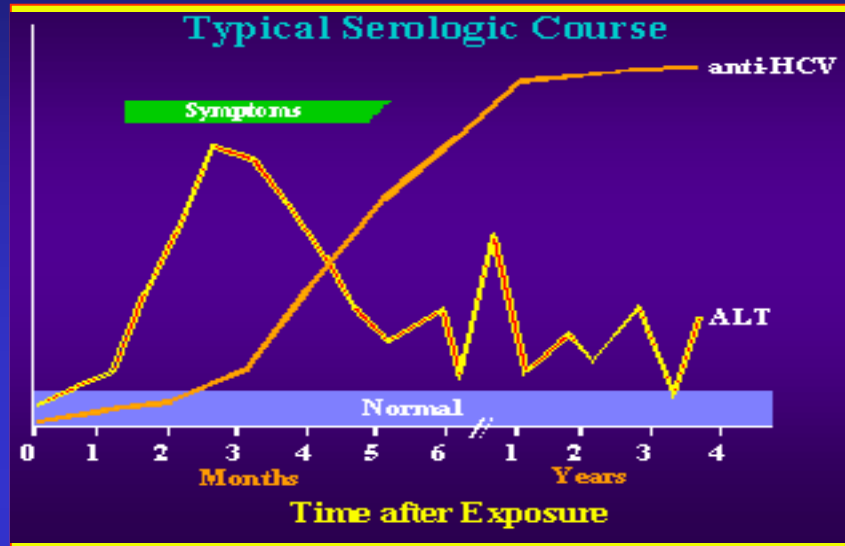
Clinical Outcomes

Acute HCV infection

✓ subclinic

✓ acute hepatitis

Outcome of Acute Hepatitis C



Healthy carrier ?

10-20%



50-85%



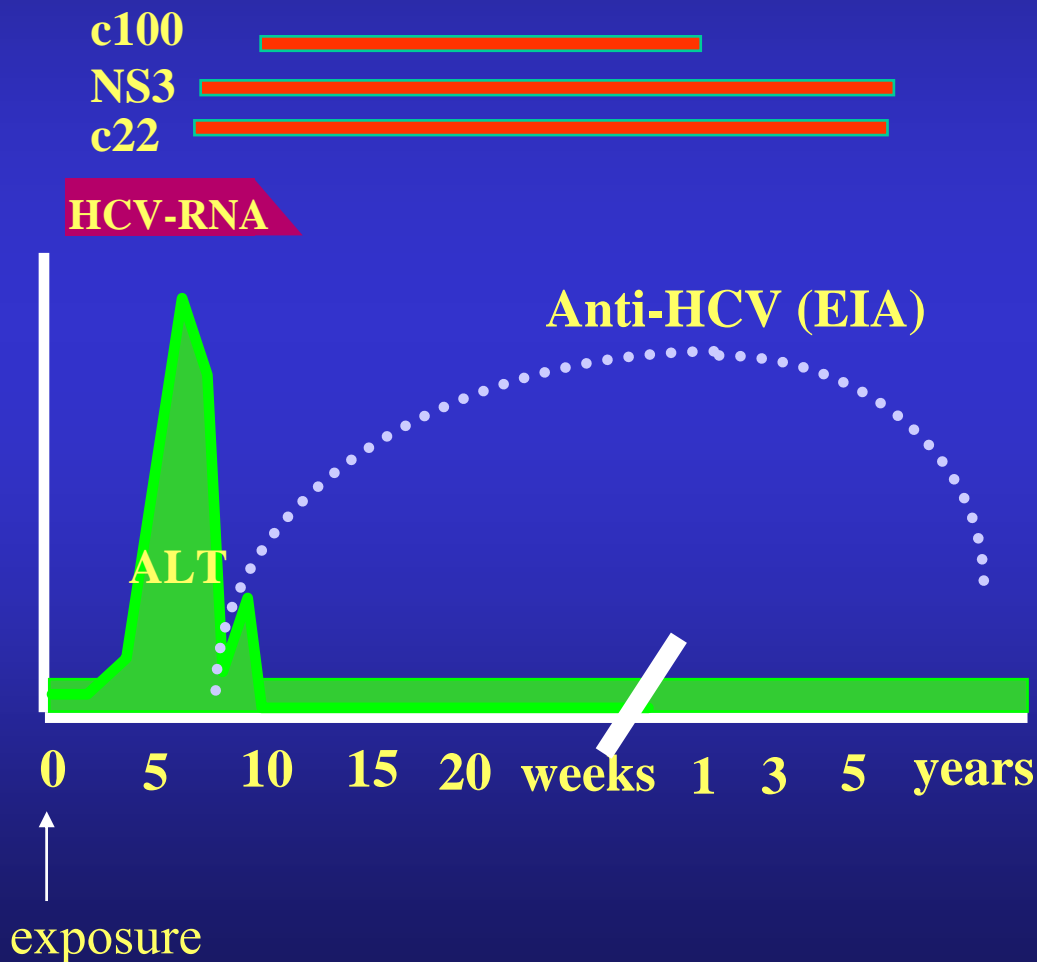
Chronic Hepatitis

15-50%



Spontaneous viral clearance

Primary HCV Infection



- ✓ HCV RNA in serum within 1-2 weeks after exposure
- ✓ Anti-HCV antibodies in serum within 3-20 weeks (average 7)
- ✓ ALT increase after 4-12 weeks
- ✓ Clinical symptoms in 10-30%
- ✓ Fulminant hepatitis is rare

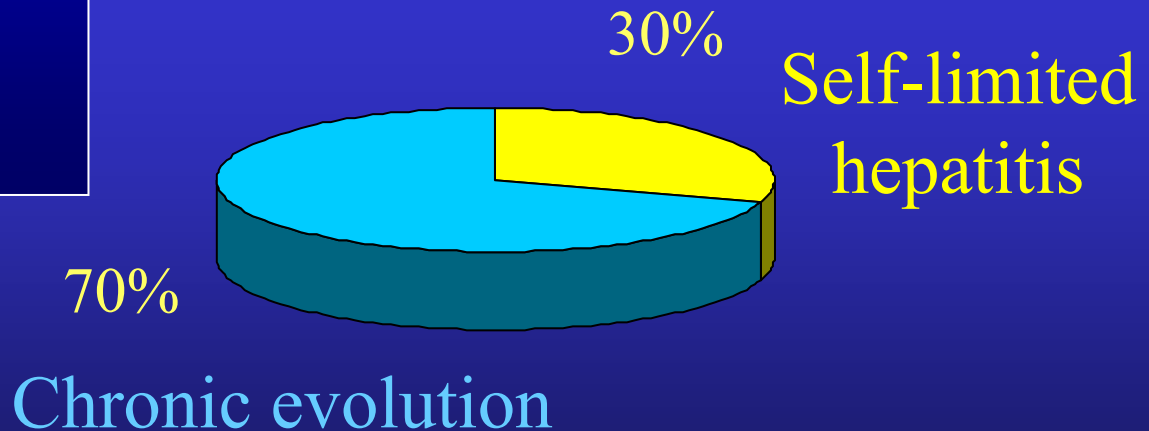
Course of Acute hepatitis C

Outcome

- Spontaneous resolution in about one third of the patients

No patients = 40

Median Follow-up = 35 months
(range 6-68)



Studies Demonstrating High Rates of Spontaneous Recovery in HCV Infection

Author	Country	% Recovery	Setting
Kenny – Walsh	Ireland	45	Contaminated Rh Ig
Wiese	Germany	45	Contaminated Rh Ig
Vogt	Germany	45	TAH* - children
Rodgers	Australia	46	Community – acquired
Gerlach	Germany	44	Symptomatic disease

Acute Hepatitis C

Factors that may influence the evolution

Virus

Quasispecies evolution

Host

Gender

Age at onset

Source of infection

Immunocompetence

Genetic profile

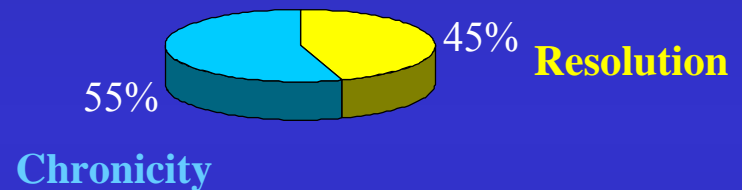
Symptomatic disease

Natural Course of Acute hepatitis C

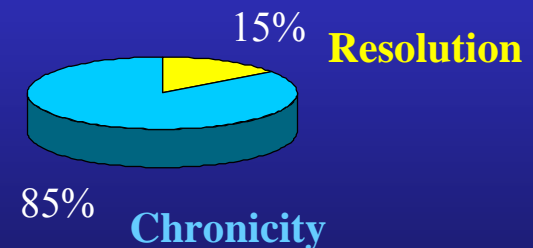
Prognostic factors

- Jaundice significantly associated with self-limited hepatitis
- No correlation with:
Genotype, Viral load at presentation, Sex, Mode of transmission

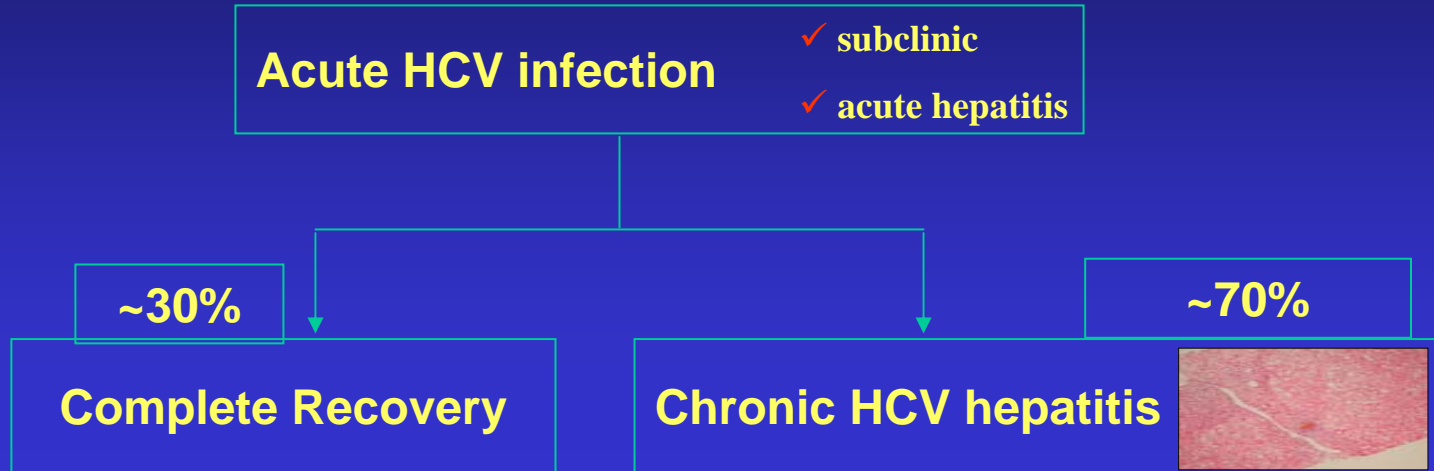
icteric AHC



anicteric AHC



Clinical Outcomes



Strategies for determining Natural History of Chronic hepatitis

Initial infection



**Early phase
Chronic hepatitis**



**Late phase chronic
Hepatitis (cirrhosis)**

20 to 40 years



Retrospective Studies



Prospective Studies



Retrospective – prospective (non – concurrent) cohort studies



Long- Term outcome of HCV infection

Retrospective Studies

Author	Country	Pts	Interval from exposure (yrs)	Cirrhosis (%)	HCC (%)	Liver Death (%)
Kiyosawa	Japan	231	10 – 29	35.1	23.4	NR
Tong	USA	131	14 – 28	51.0	10.6	15.3
Yano	Japan	70	NR [^]	50.0	NR	NR
Niederau	Germany	838	9 – 22	16.8	2.0	3.7
Gordon*	Usa	215	19	55.0	3.7	NR
Gordon**	Usa	195	20	21.0	1.0	NR

mean 42%

* Transfusion ; ** Community – Acquired; ^ Not reported

Long- Term outcome of HCV infection

Prospective Studies

Author	Country	Pts	Interval from exposure (yrs)	Cirrhosis (%)	HCC (%)	Liver Death (%)
Di Bisceglie	USA	65	9.7	12.3	0	3.7
Koretz	USA	80	16.0	7.0	1.3	1.3
Mattson	Sweden	61	13.0	8.0	NR	1.6
Tremolada	Italy	135	7.6	15.6	0.7	3.7

mean 11%

Long- Term outcome of HCV infection

Retrospective – Prospective Studies

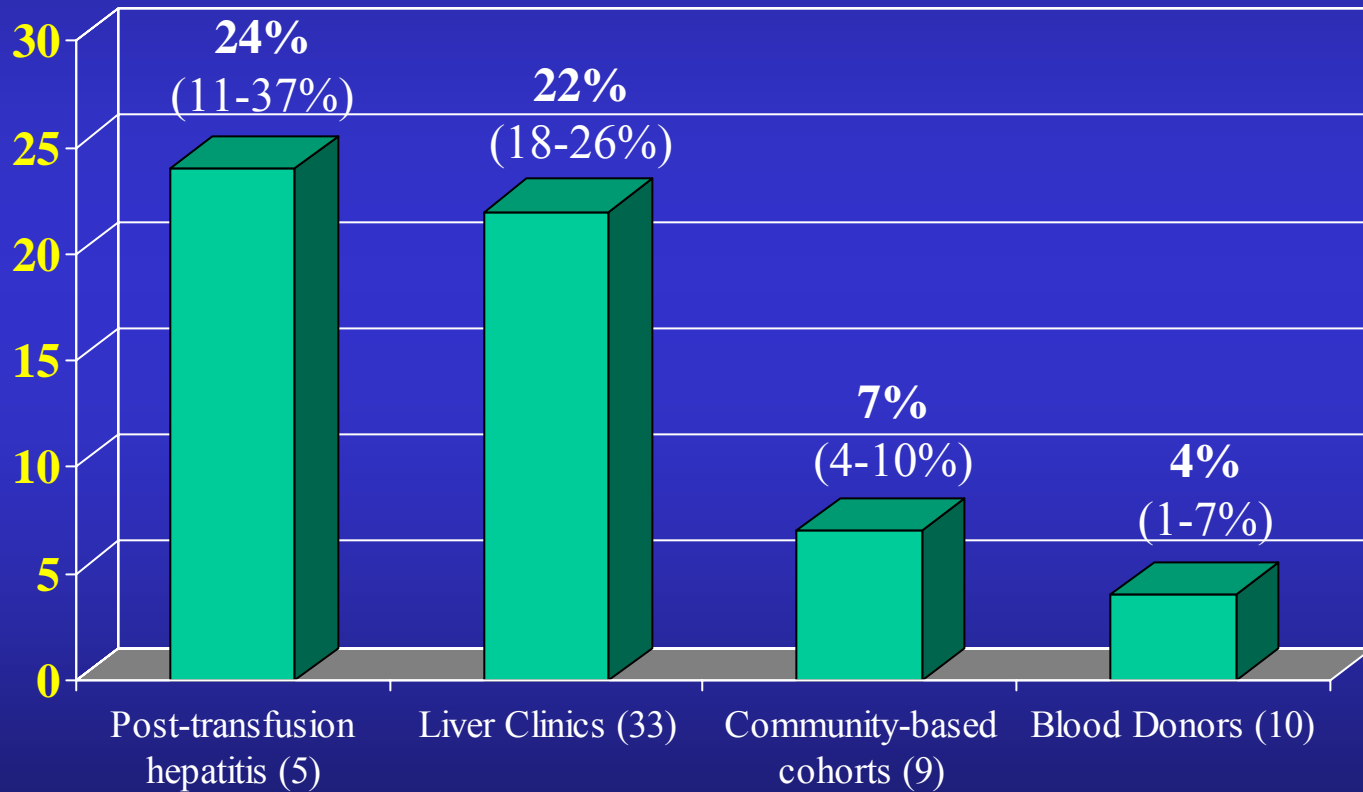
Author	Group	Pts	Interval from exposure (yrs)	Cirrhosis (%)	HCC (%)	Liver Death (%)
Vogt	Children	67	17	1.5	0	0
Kenny-Walsh	Young women	376	17	2.0	0	0
Wiese	Young women	917	20	0.4	0	0
Seeff*	Young men	17	45-50	5.9	0	5.9
Thomas	IDU	919	9	4.5	0	3.8
Rodgers	Comm acq	95	25	6.0	0	1.0
Seeff**	PTH	222	23	15.0	1.9	4.1

Note: The interval from exposure (yrs) column is circled in red. A bracket on the right indicates that the cirrhosis percentages for the first six studies are <6%.

*Community-acquired **Transfusion

Progression to cirrhosis after 20-year HCV infection by study recruitment

57 studies



Mean age

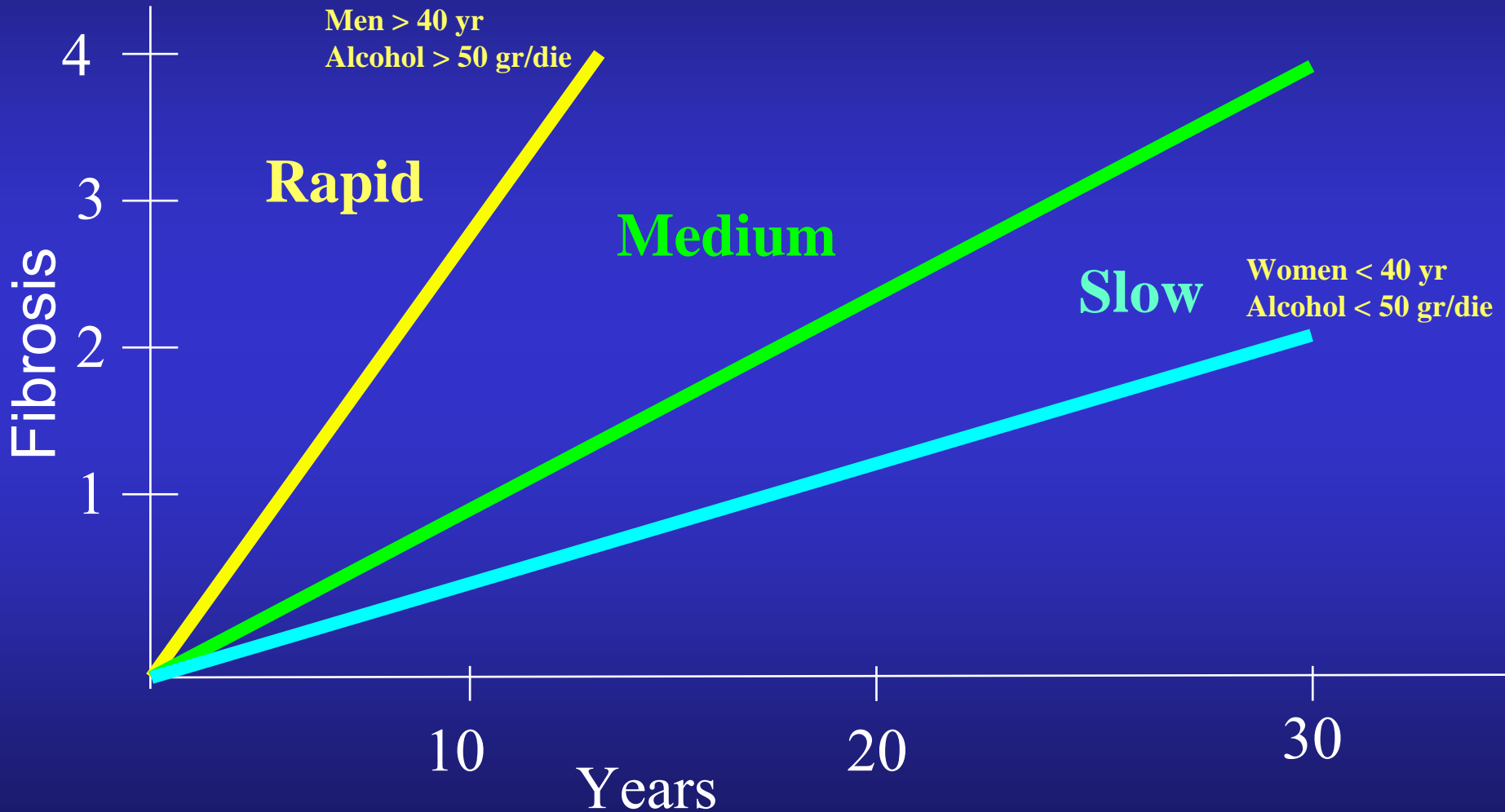
42

29

26

22

PROGRESSION OF HEPATIC FIBROSIS IN CHRONIC HEPATITIS C



Potential Cofactors As Determinants of Disease Progression

Viral factors

Viral Load
Viral Genotype
Multiplicity of quasispecies

Host Factors

Age at infection
Gender
Duration of infection
Disease expression
Immune deficiency
Genetic susceptibility
Coinfections (HIV, HBV)
Co-morbid conditions
e.g., hemochromatosis, non alcoholic steatohepatitis, ...

External Factors

Alcohol abuse
Diet
Smoking
Drugs
Hepatotoxins
Environmental contaminants

HCV: natural history

Alcohol

- Increased risk of cirrhosis in HCV-infected patients who drink 30-60g alcohol per day
- Sustained virological response to IFN is lower in patients with a recent history of alcohol abuse
- Increased quasispecies and viremia levels in alcoholics
- Alcohol and HCV are synergistic in accelerating hepatic fibrosis in patients through immune related reactions and increased oxidative stress

HCV: natural history

- HBV coinfection:

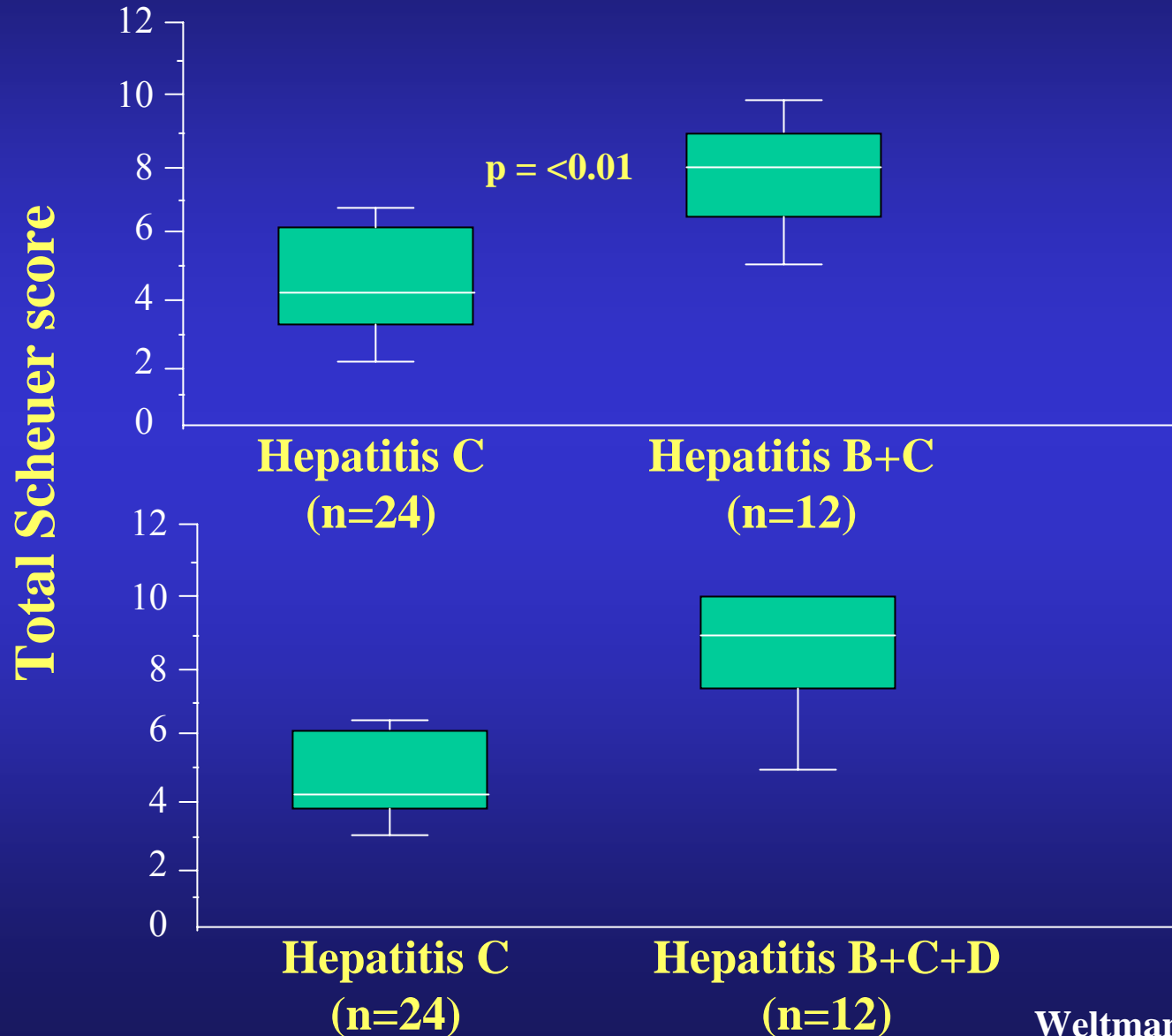
→ More severe liver damage

→ More rapid clinical course

→ High risk for HCC

→ Lower IFN therapy response

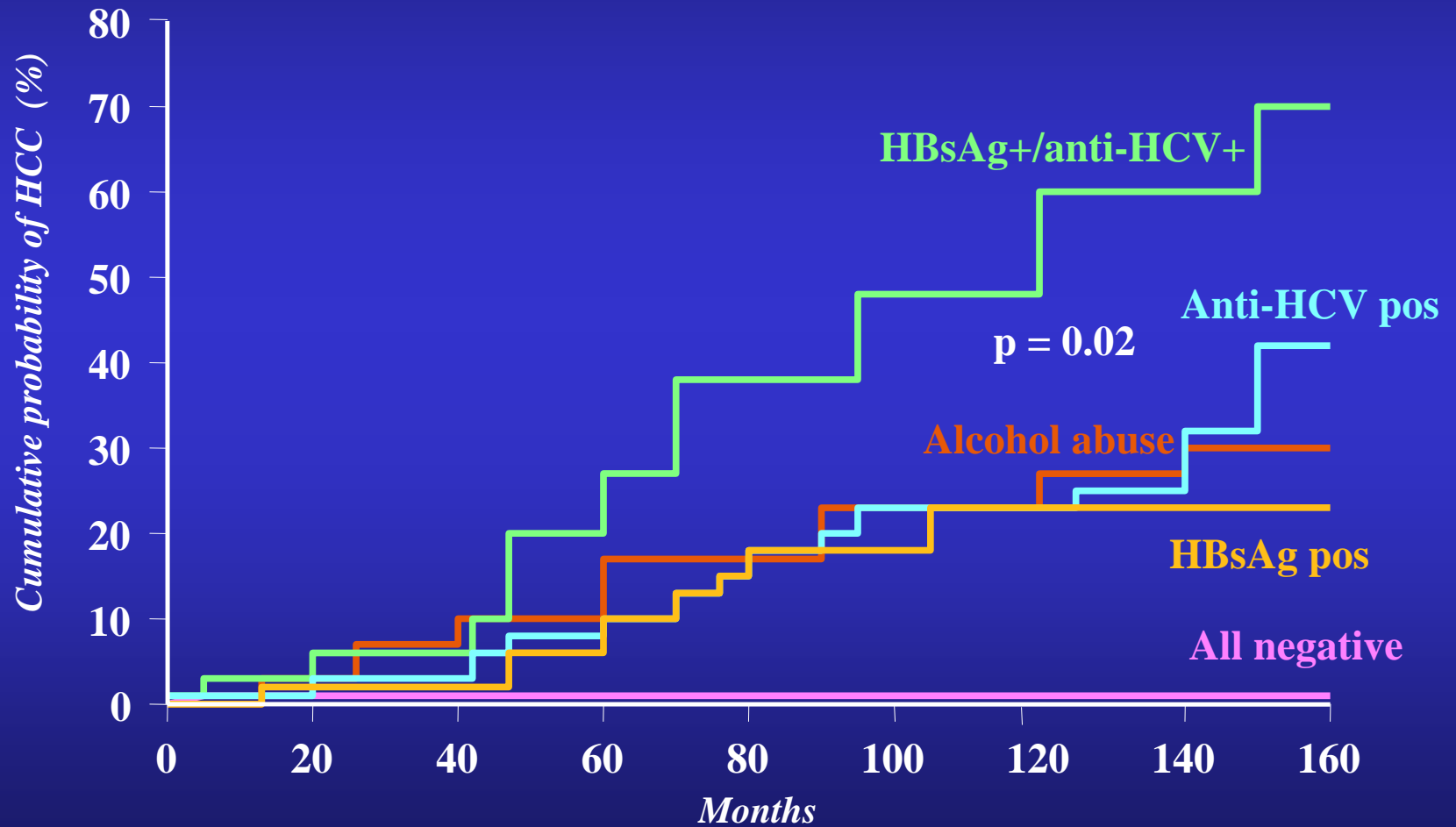
Liver histopathology in patients with hepatitis B/C and hepatitis B/C/D compared with matched control subjects with HCV alone



Risk for HCC according to Alcohol Intake and the Presence of HCV and HBV Infection

	Alcohol intake (g/day)			
	0-60		> 60	
	Cases/Controls (no.)	O.R.	Cases/Controls (no.)	O.R.
Neither	30/412	-	157/335	7.0
HCV infection	95/21	55.0	76/11	109.0
HBV infection	41/27	22.8	51/17	48.6

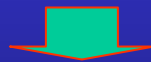
Rates of HCC in Relation to Etiology of Cirrhosis



Occult HBV infection in patients with chronic hepatitis C

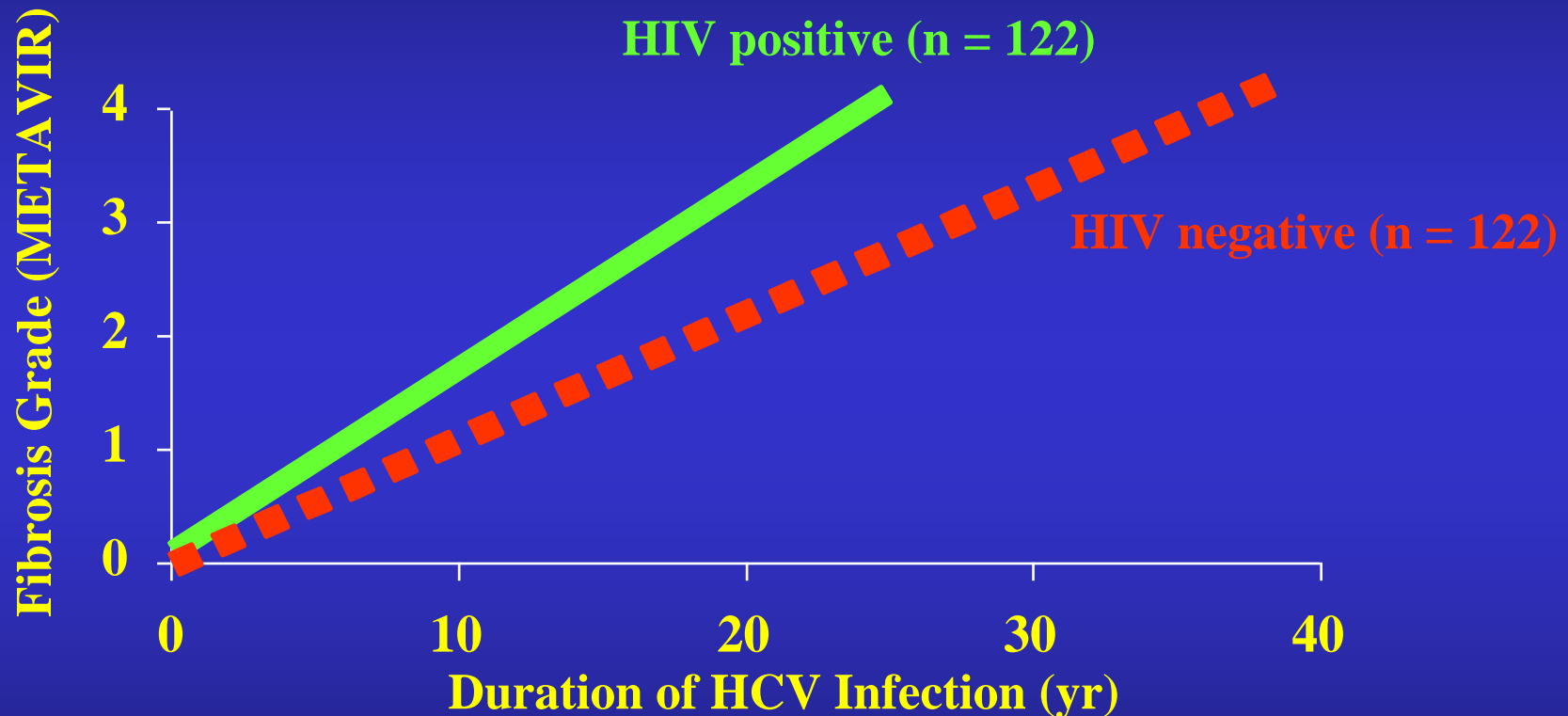
Pts = 200 HCV positive

	Liver HBV DNA		<i>p</i>
	Positive N=66 (33%)	Negative N=134	
Anti-HBc positive	46		
Anti-HBc negative	20		
<i>Histologic findings</i>			
Minimal changes	0	5 (4%)	<i>ns</i>
Chronic hepatitis	44 (67%)	103 (77%)	<i>ns</i>
Cirrhosis	22 (33%)	26 (19%)	0.04



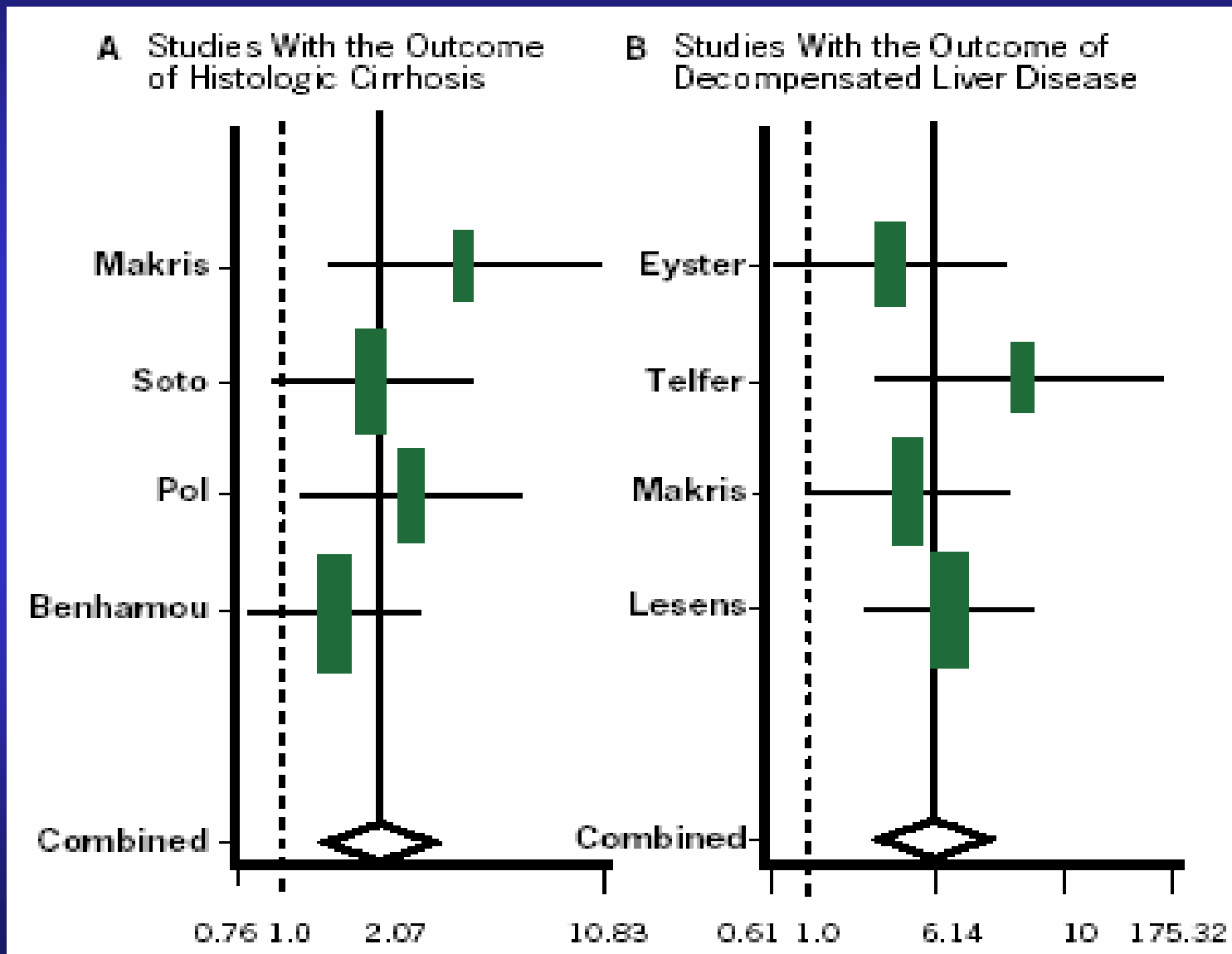
Occult HBV infection may interfere with the clinical outcome of chronic hepatitis C and favor or accelerate the evolution to cirrhosis

Liver Fibrosis Progression: Influence of HIV Coinfection



Patients matched for sex, risk factors, age, age at HCV contamination, age at liver biopsy and daily alcohol consumption.

Increased Risk of Cirrhosis and ESLD in HIV/HCV-Coinfected Patients.



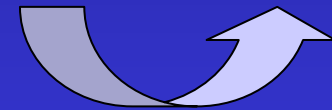
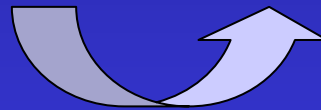
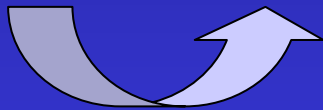
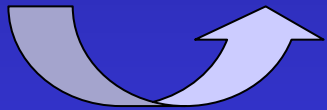
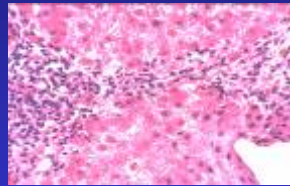
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F1

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F4



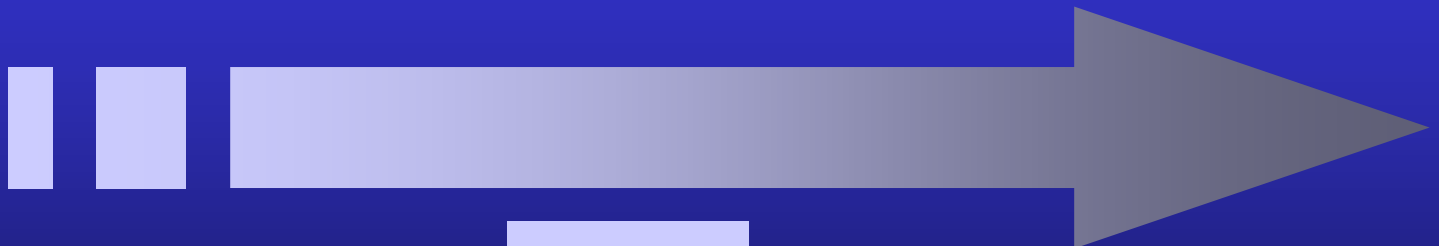
4- 6 anni

10- 15 anni

10-15 anni

4- 6 anni

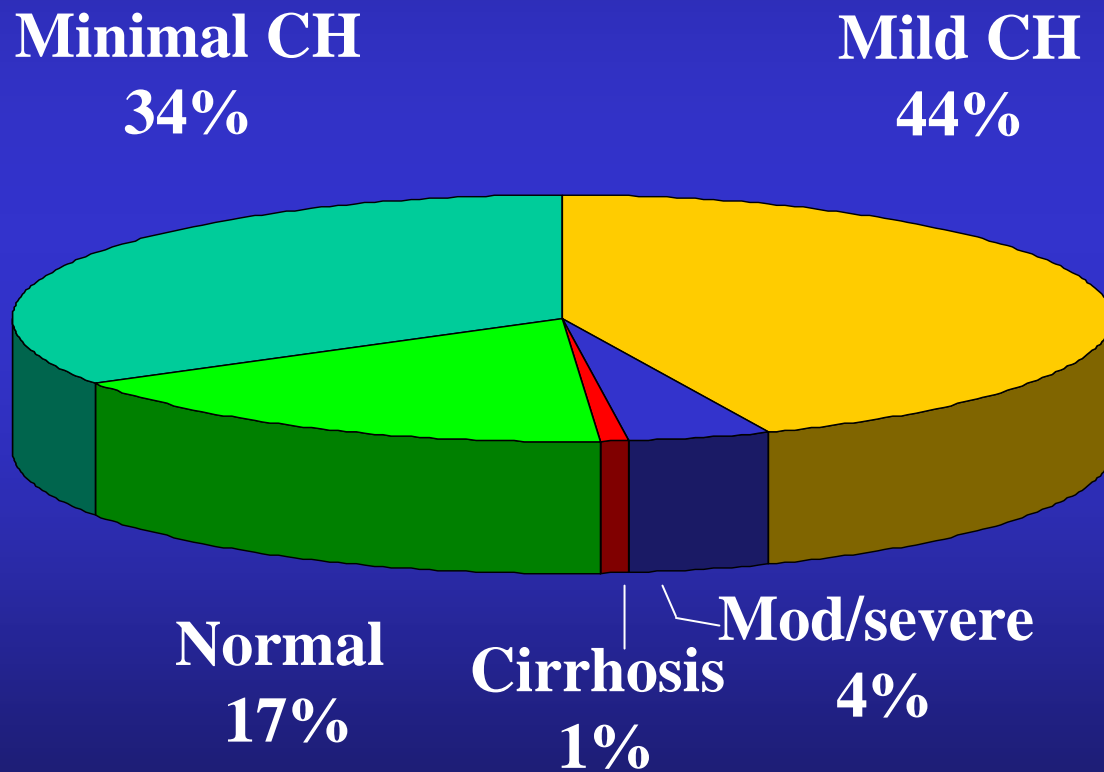
**Coinfezione
HIV-HCV
CD4 < 500**



5 anni

Liver histology among 159 HCV carriers with persistently normal ALT*

(Italian prospective study of the asymptomatic C carriers)



* (ALT every 3 months over a 12-month period)

Predictive Value of ALT Levels for Histologic Findings in Chronic Hepatitis C: a European Collaborative Study

METAVIR Fibrosis Score

	0	1	2	3	4
Normal ALT	35%	52%	12%	0	2%
Elevated ALT	1%	24%	51%	17%	8%

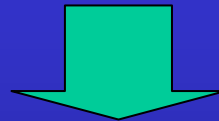
0= no fibrosis, 1= portal fibrosis without septa, 2= portal fibrosis with few septa, 3= septal fibrosis without cirrhosis, 4= cirrhosis

Natural history of HCV carriers with persistently normal ALT

Prospective studies with histological follow-up

Persico et al Gastroenterology 2000

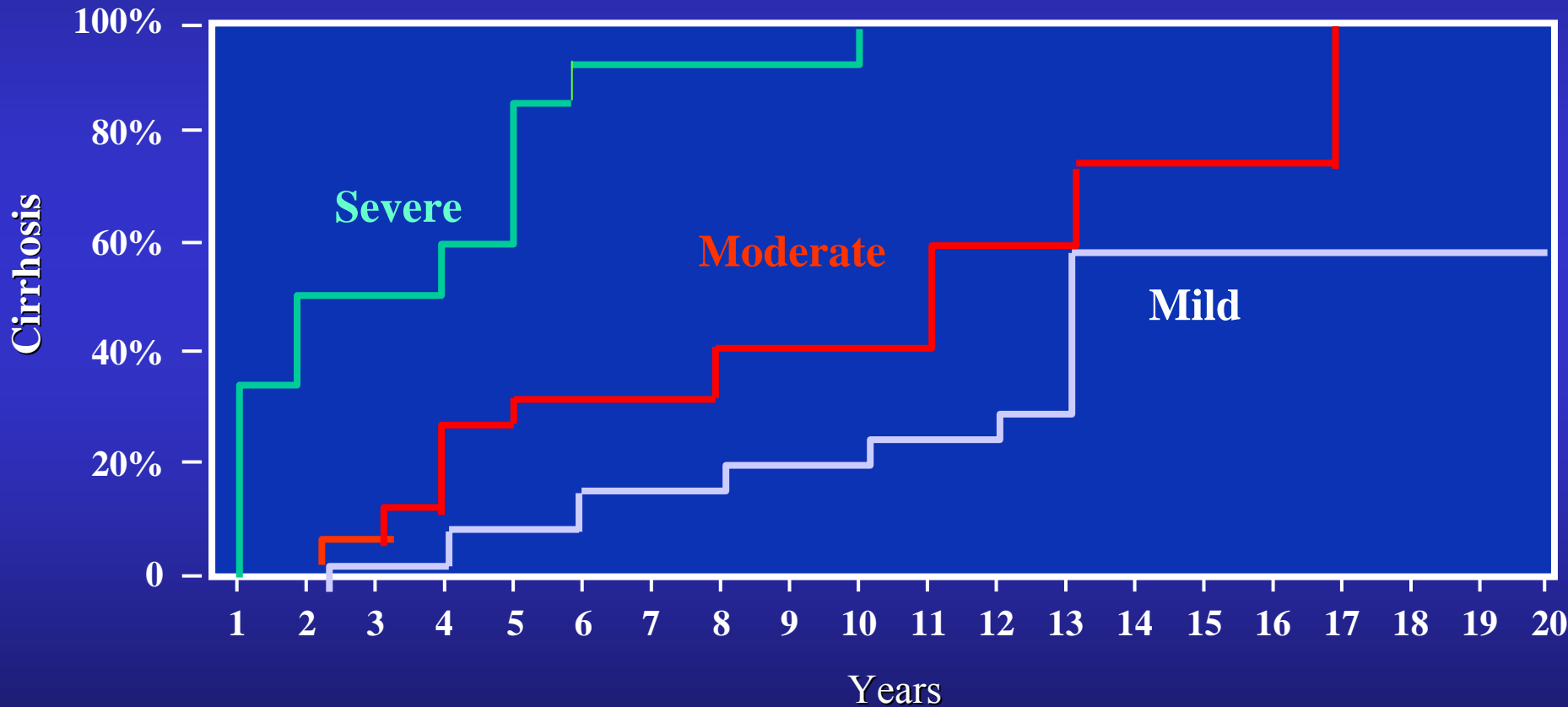
Martinot-Peignoux et al Hepatology 2001



Very slow or no fibrosis progression

Chronic Hepatitis C: Progression to Cirrhosis

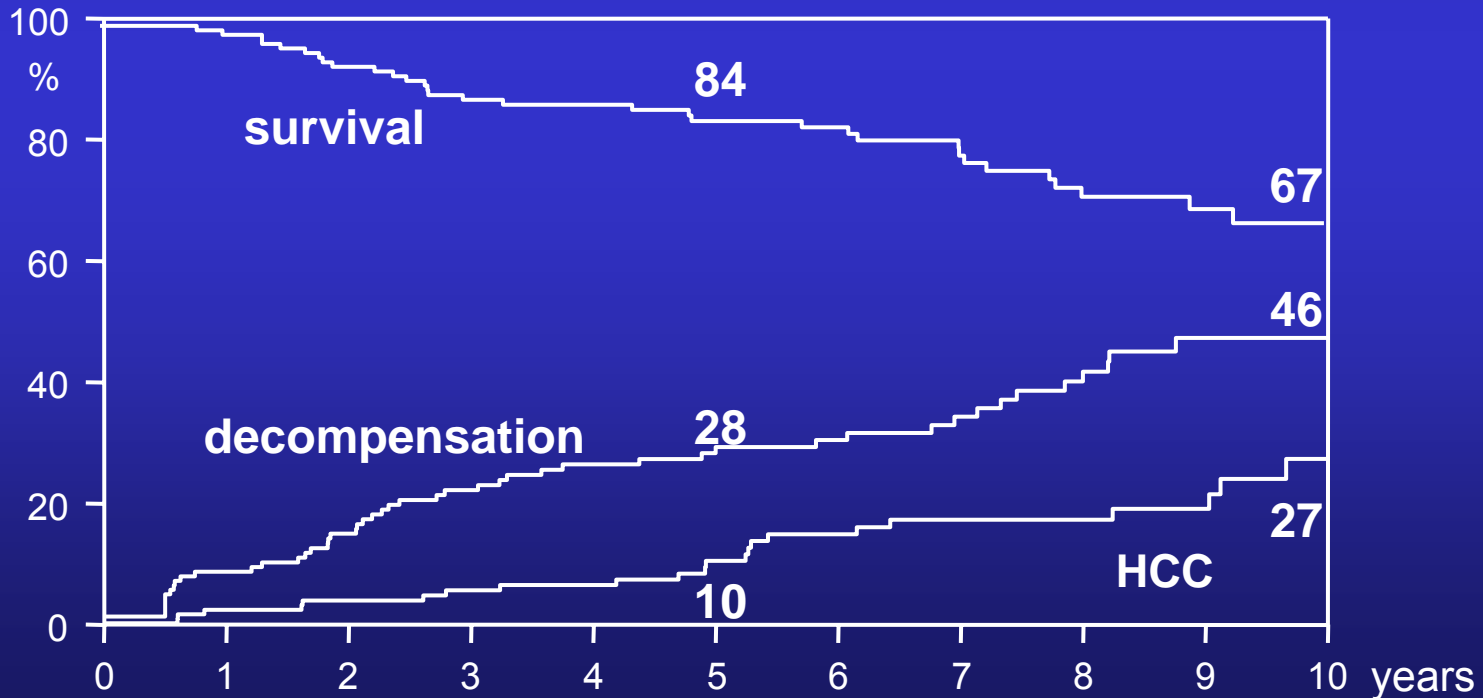
- Baseline Fibrosis



Adapted from Yano M et al. Hepatology. 1996;23:1336.

Survival in compensated cirrhosis C

Reference	Area	Pts (n)	Median age (yrs)	Median follow-up (yrs)	5-year survival
Niederrau 1998	Germany	141	58	4.2	85
Hu 1999	U.S.A.	112	52	4.5	83
Degos 2000	France	416	57	5.6	85
Eurohep 2002	Europe	136	58	6.8	84



Compensated cirrhosis type C

independent factors affecting survival
multivariate analysis (Cox's model)

Factors	prognosis worse if	p value
● age	older	0.01
● gender	male	0.01
● albumin	< 35 g/l	0.0001
● bilirubin	> 17 ≤ 51 μmol/l	0.0000
● platelets	< 130 x 10 ⁹ /l	0.006
● oesophageal varices	present	0.001

Fattovich et al Gastroenterology 1997; 112: 463-472

Degos et al Gut 2000; 47: 131-136

Development of decompensation in HCV-related cirrhosis

(ascites, jaundice, encephalopathy, variceal bleeding)

Reference	Area	patients (no.)	Child's grade	Mean follow-up (yrs)	Incidence 100 person/yrs	4 to 5 yrs risk (%)
1. Eurohep	Europe	136	A	6.8	5.3	28
2. Serfaty	France	103	A/B	3.3	5.5	20
3. Hu	U.S.A.	112	A/B	4.5	4.8	22

1. Am J Gastroenterol 2002; 97: 2886-2895
2. Hepatology 1998; 27: 1435-40
3. Hepatology 1999; 29: 1311-6

Incidence of HCC in HCV-related Cirrhosis

Authors	Country	3 yrs	5 yrs	10 yrs
Fattovich 1997	Europe	3%	7%	14%
Chiaramonte 1999	Italy	7%	20%	28%
Benvegnù 1994	Italy	2.8%	11.5%	30%
Ikeda 1993	Japan	10%	21%	53%
Yoshida 1999	Japan	12.5%	20%	60%

Clinical Outcomes

