“ Malattie del fegato e invecchiamento “

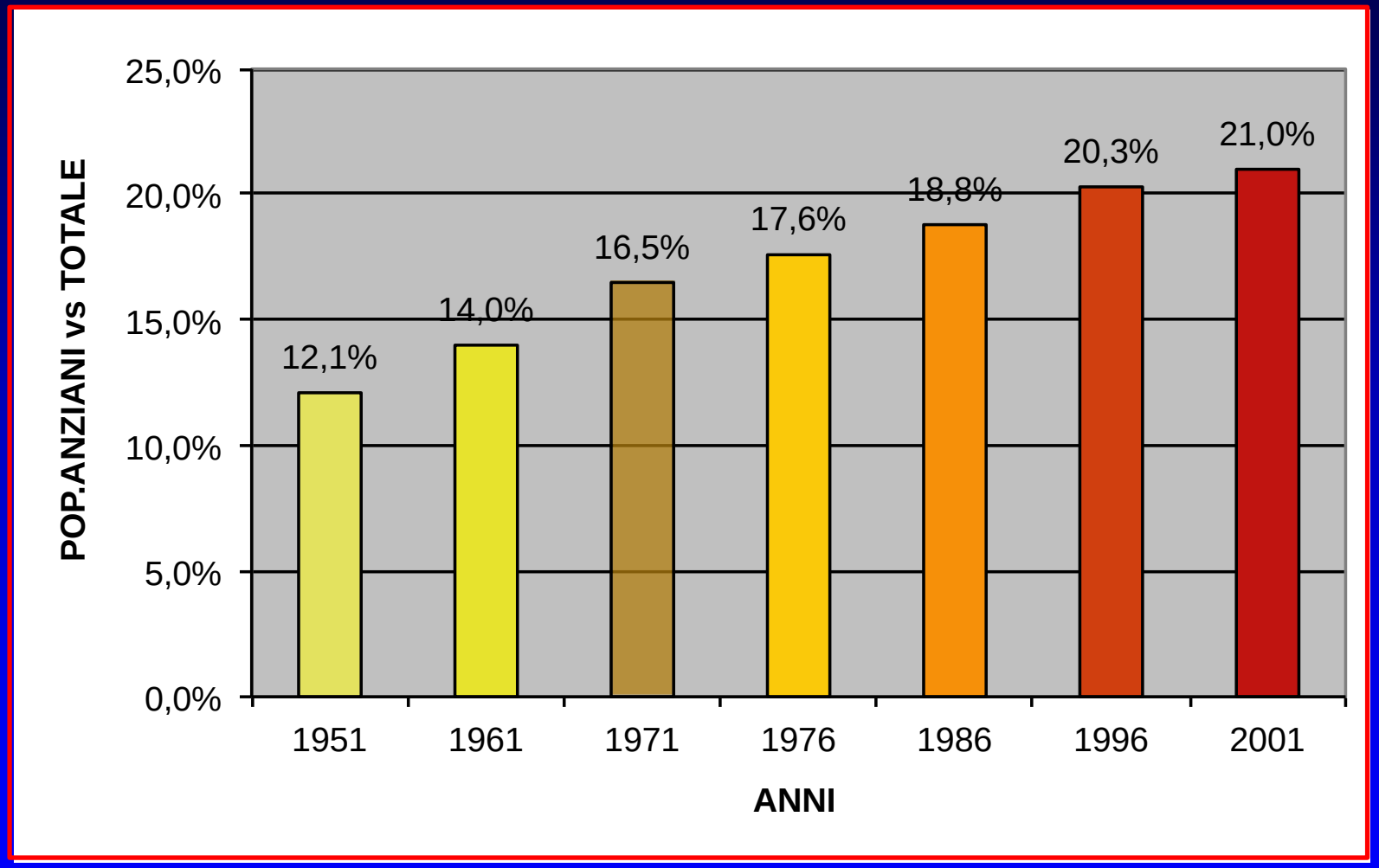
E. Villa

Università di Modena e Reggio Emilia; Azienda Ospedaliero-Universitaria Modena

Modena, 12 Dicembre 2012

UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

ANDAMENTO DELL'INVECCHIAMENTO nella POPOLAZIONE ITALIANA



B.Giraldi

MODIFICAZIONI NELL'ORGANISMO DELL'ANZIANO

MODIFICAZIONI MORFOLOGICHE

MODIFICAZIONI FISIOLOGICHE

MODIFICAZIONI BIOCHIMICHE

MODIFICAZIONI PSICOLOGICHE

Invecchiamento di fegato

- Ridotta rigenerazione epatociti
- Decremento della massa epatica del 20%
- Ridotta sintesi di proteine
- Ridotto metabolismo di farmaci

  - Accumulo farmaci
  - Necessità di adeguare le dosi all'età, alla funzionalità epatica e allo stato di salute

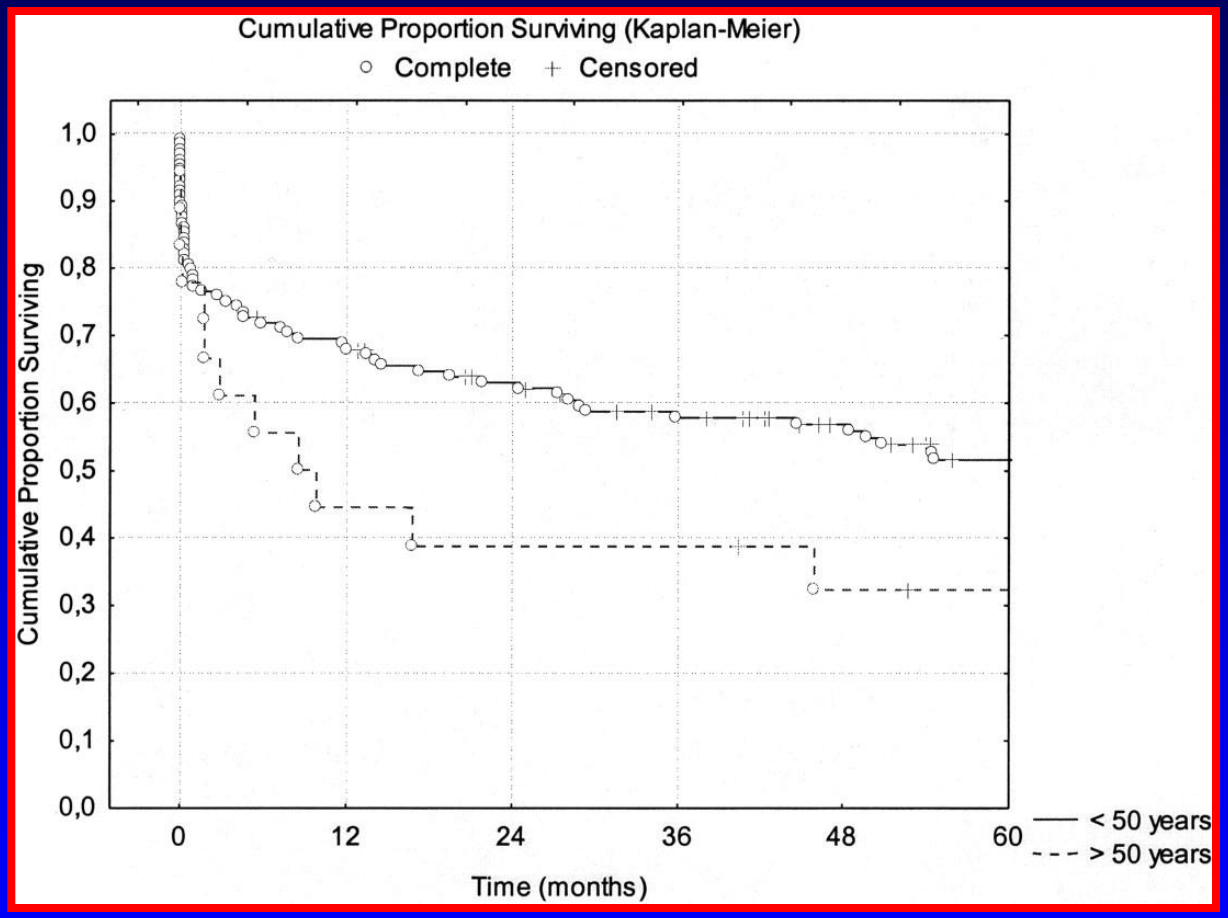
Invecchiamento ed epatopatie

Dati epidemiologici

Effetto dell'invecchiamento

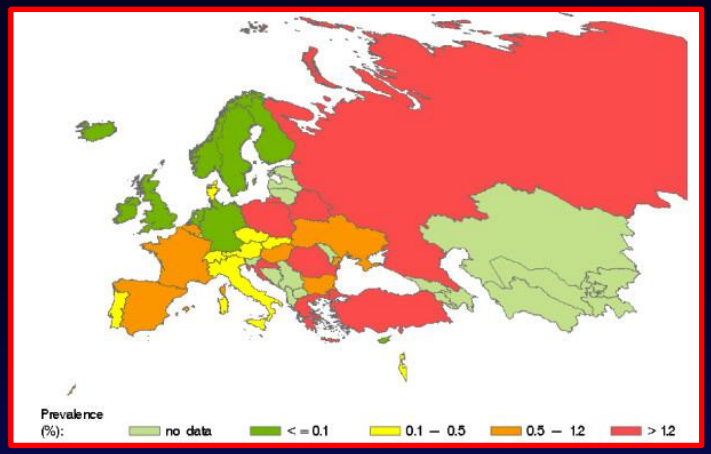
- sulla gravità del danno epatico
- sulla progressione della fibrosi
- sulla terapia

Cumulative survivalg for HCV recipients transplanted with livers from older or younger than 50 years

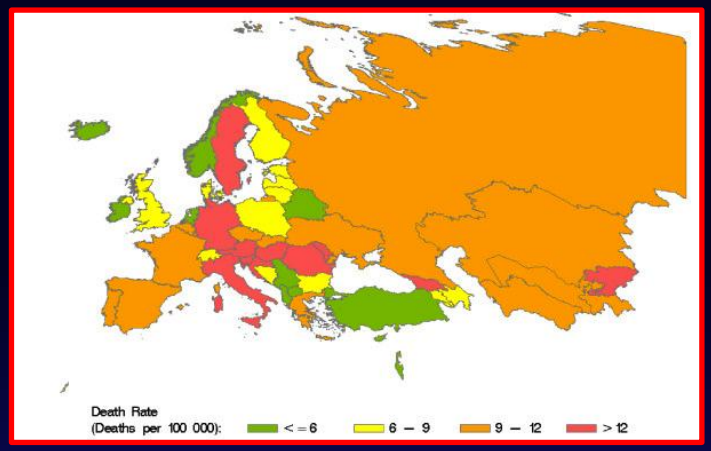


Boin et al, Transplantation Proc 2008

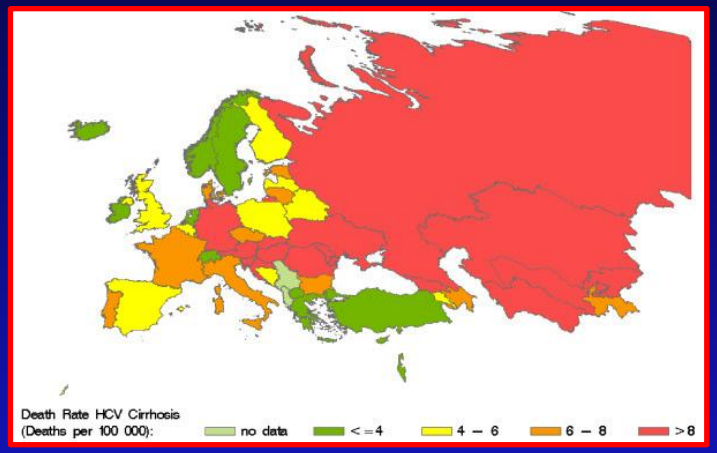
HCV-related burden of disease in Europe: a systematic assessment of prevalence, morbidity, and mortality



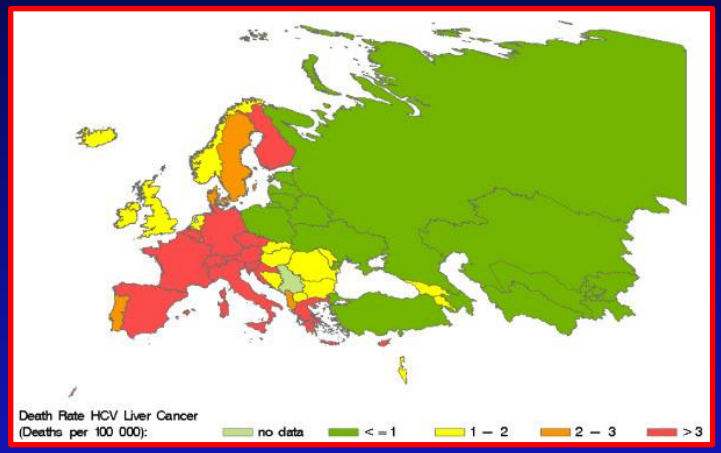
Prevalence of HCV infection



HCV-related death rates



Death rates for HCV-related liver cancer



Death rates for HCV-related liver cancer

Mühlberger et al. BMC Public Health 2009

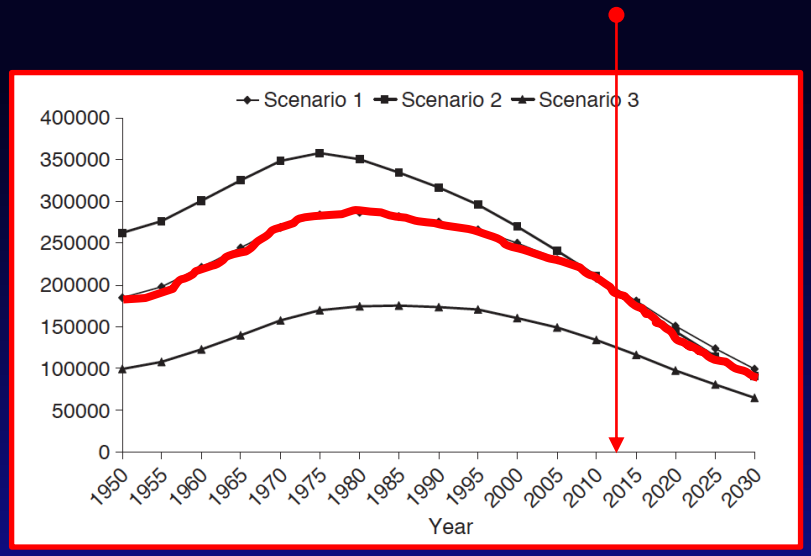
Anti-HCV prevalence in studies conducted in the general population of different Italian areas, by geographical area and decade of birth.

Decade of birth	Anti-HCV prevalence (%) in studies conducted in northern and central Italy			Anti-HCV prevalence (%) in studies conducted in southern Italy and major Italian islands (Sicily and Sardinia)		
	Median (range)	Mean	Weighted mean[a]	Median (range)	Mean	Weighted mean[a]
1980–89	0 (0–0)	0	0	0.5 (0–1.4)	0.6	0.4
1970–79	0.5 (0.2–1.4)	0.6	0.7	0.6 (0–2.7)	0.9	0.9
1960–69	1.4 (0.4–5)	1.7	1.3	1.3 (0–5.3)	2.1	2.2
1950–59	1.9 (0.6–3)	2	1.9	3.4 (1.5–9.4)	4.7	4.3
1940–49	5.6 (3.5–10)	6.5	5.2	17.3 (7.5–20.7)	16.3	15.5
1930–39	10 (4–19)	11	9	32.6 (13–45)	30	27
1920–29	6 (4–23)	10	6	38 (18–49)	36	33
1910–19	7 (4–10)	7	5	36 (23–40)	34	32

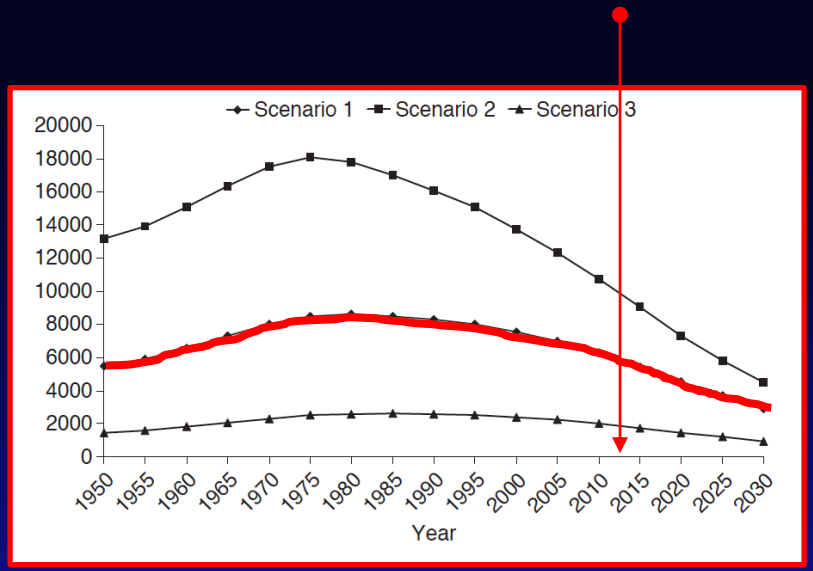
[a] Weighted for the sample size of each study.

Mariano et al., Scandinavian Journal of Infectious Diseases, 2009

Estimating the incidence, prevalence and clinical burden of hepatitis C over time in Italy



Estimated number of individuals living with HCV-related liver cirrhosis

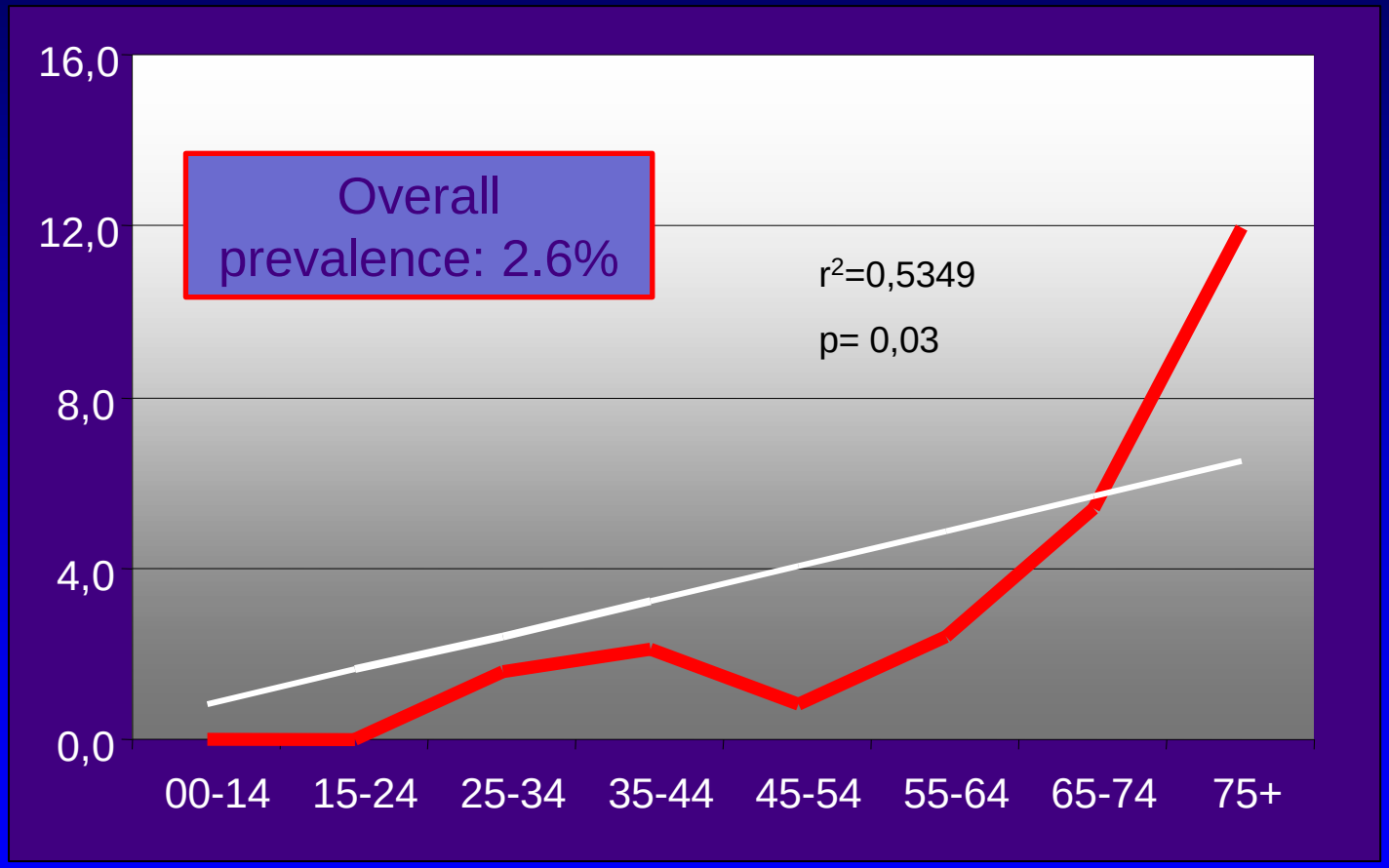


Estimated number of HCV related deaths from hepatic causes

Mariano et al., Scandinavian Journal of Infectious Diseases, 2009

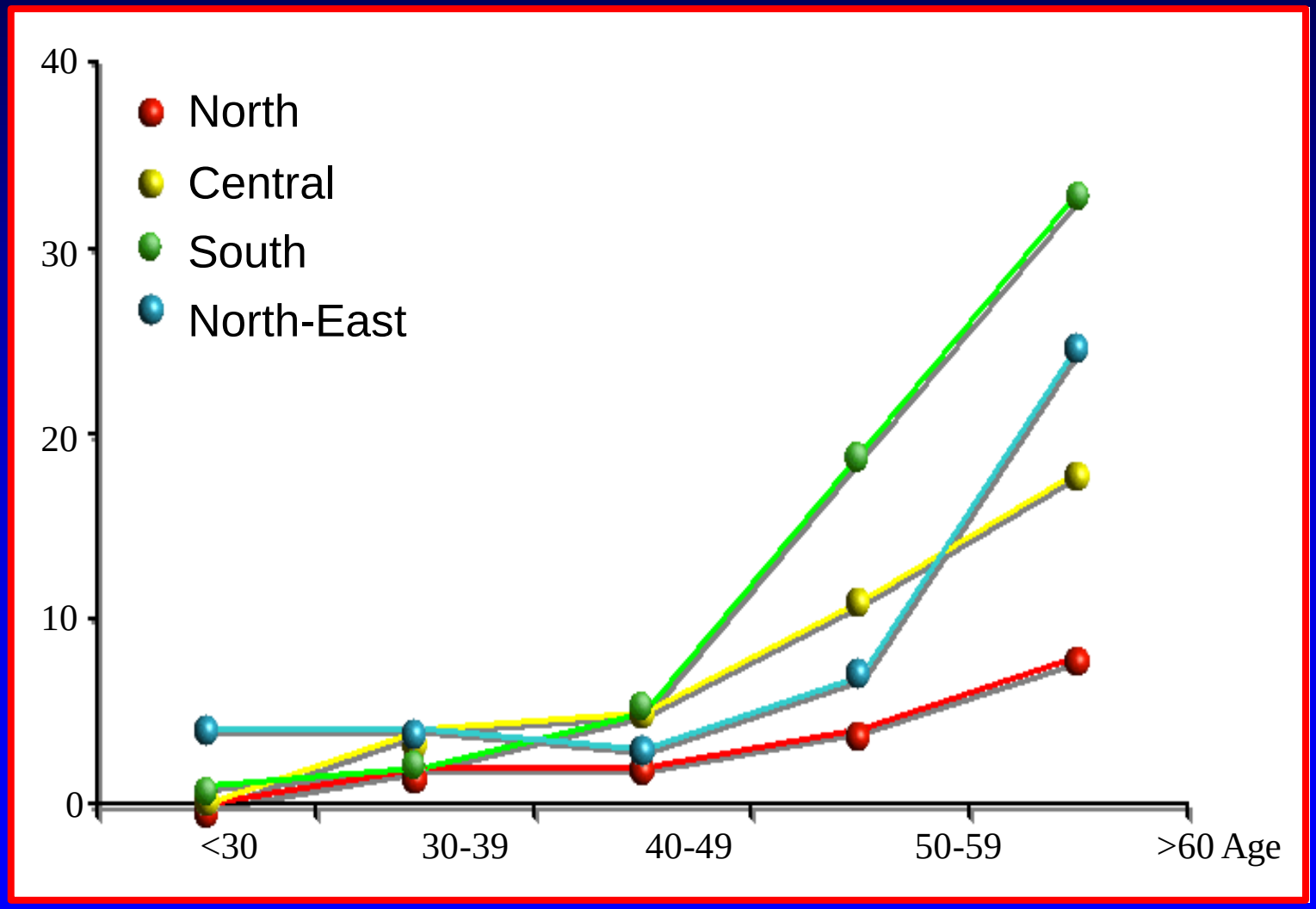
Anti-HCV seroprevalence according to age

Vicenza study

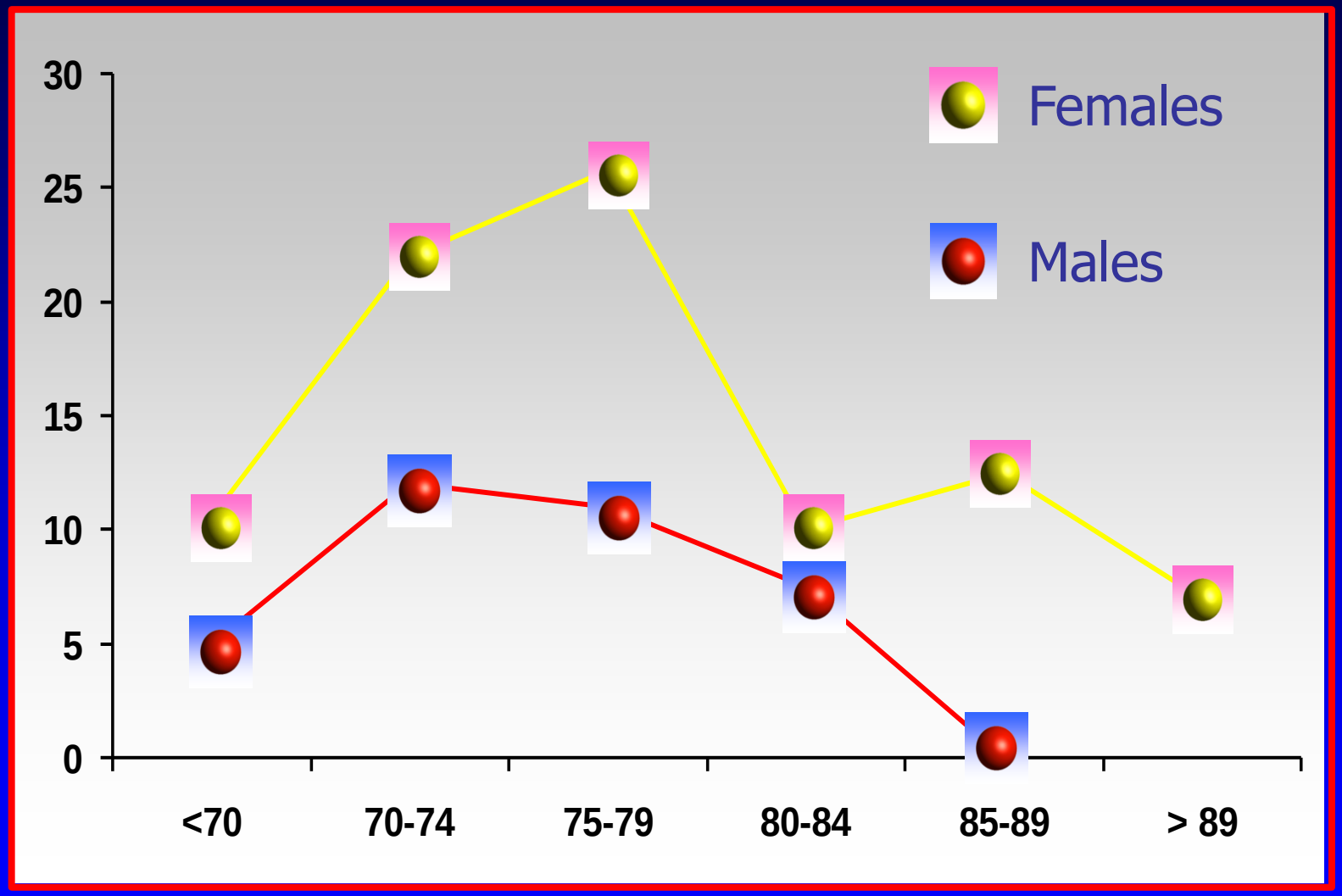


Fabris P et al, J Clin Gastroenterol 2008

Infezione da HCV



Prevalenza di antiHCV a seconda della classe di età e sesso



Baldo V, Floreani A et al, Gerontology 2000

Invecchiamento ed epatopatie

Dati epidemiologici

Effetto dell'invecchiamento

- sulla gravità del danno epatico
- sulla progressione della fibrosi
- sulla terapia

Infezione da HBV

- Gli anziani che si infettano con HBV spesso sviluppano un'epatite subclinica od oligosintomatica con un basso rate di clerance dell'HBV, per alterazione del loro stato immunologico
- Questo comporta la possibilità di rimanere portatori cronici con alta infettività (HBeAg+) ma sostanzialmente asintomatici

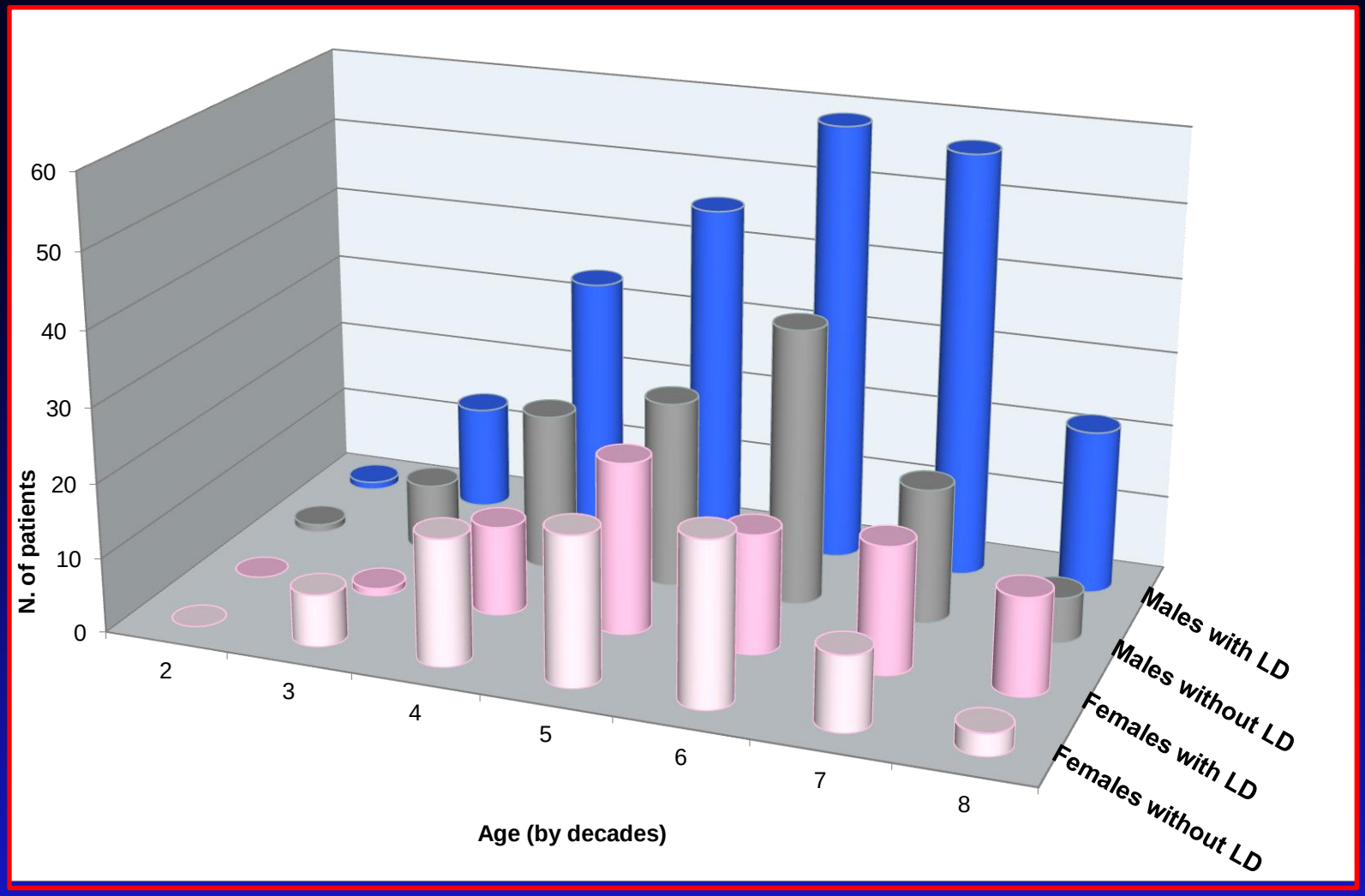
Chiaramonte M, Floreani A, J Med Virol 1982
Floreani A, Chiaramonte M, Arch Int Med 1983

HBV-DNA+ in bambini HBsAg+ in area ad alta endemia (Camerun)

Età (aa)	Maschi (n. 86)	Femmine (n.77)
4-7	35.3%	18.2%
7-9	35.3%	12.0%
10-14	26.5%	14.3%
Tot.	31.8%	14.1%

Rapicetta, Chiaramonte et al, 1991

Presence/Absence of Chronic Hepatitis B by gender and age



Brunetto MR, Roma 2012

Prevalence of Cirrhosis by age

Age years	**Prevalence Variation**	**Females**	**Males**	**Prevalence Variation**
<30		**0/8**	**0/26**	
31-40		1/31 **(3.2%)**	3/56 **(5.4%)**	
41-50		3/43 **(7.0%)**	8/72 **(11.1%)**	
51-60	≅ ≈ 4.5 x	3/38 **(7.9%)**	25/96 **(26.0%)**	≈ 2.5 x ≈ 2 x
61-70	≈ 1.3 x	10/27 **(37%)**	38/75 **(50.7%)**	≈ 1.4 x
71-80		8/16 **(50%)**	20/28 **(71.4%)**	

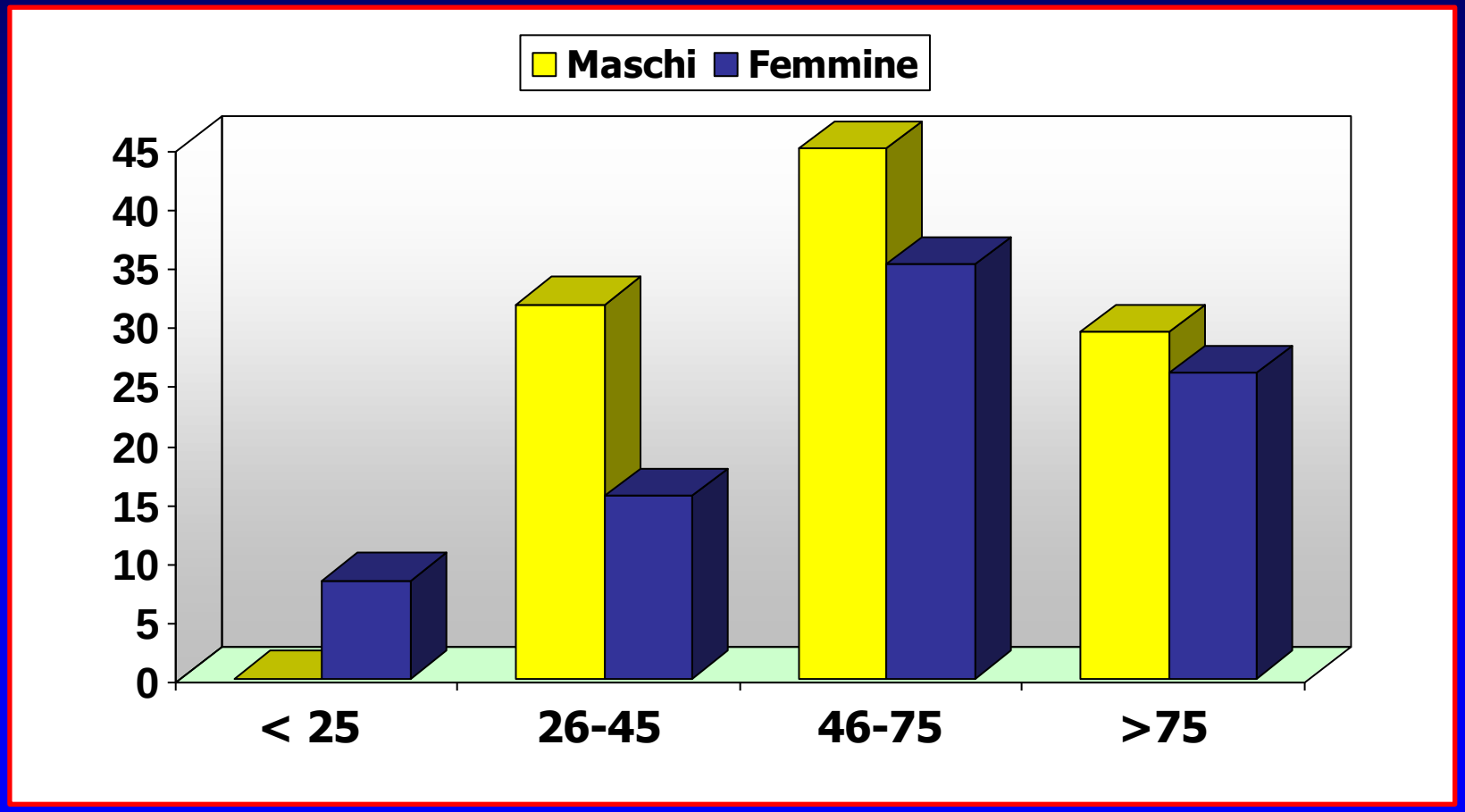
Brunetto MR, Roma 2012

AIH: clinical features of patients with onset in geriatric age (>65 yrs) and in adult life

	<65 yrs	>65 yrs	P-value
N. Pts	57	16	
N. with acute onset	16 (28%)	11 (68.7%)	<0.05
Female (%)	89.9	86.7	n.s.
Mean grade	5.83 ± 0.96	5.41 ± 0.61	n.s.
Mean stage	4.62 ± 1.08	5.47 ± 0.62	<0.003
AST (U/L)	426 ± 454.6	629 ± 497	n.s.
ALT (U/L)	513 ± 499	689 ± 640	n.s.
IgG (mg/dl)	2240 ± 984	2287 ± 875	n.s.
IgA (mg/dl)	306 ± 173	362 ± 256	n.s.
IgM (mg/dl)	175 ± 122	69 ± 16	n.s.
PT (%)	73.6 ± 17.6	69.5 ± 16.8	n.s.

Floreani A et al ATP, 2006

Prevalenza di steatosi ecografica in rapporto all'età



Chiaramonte et al. Studio Arsita 2 2

Prevalence ase (NAFLD)

Shimizu, 2007

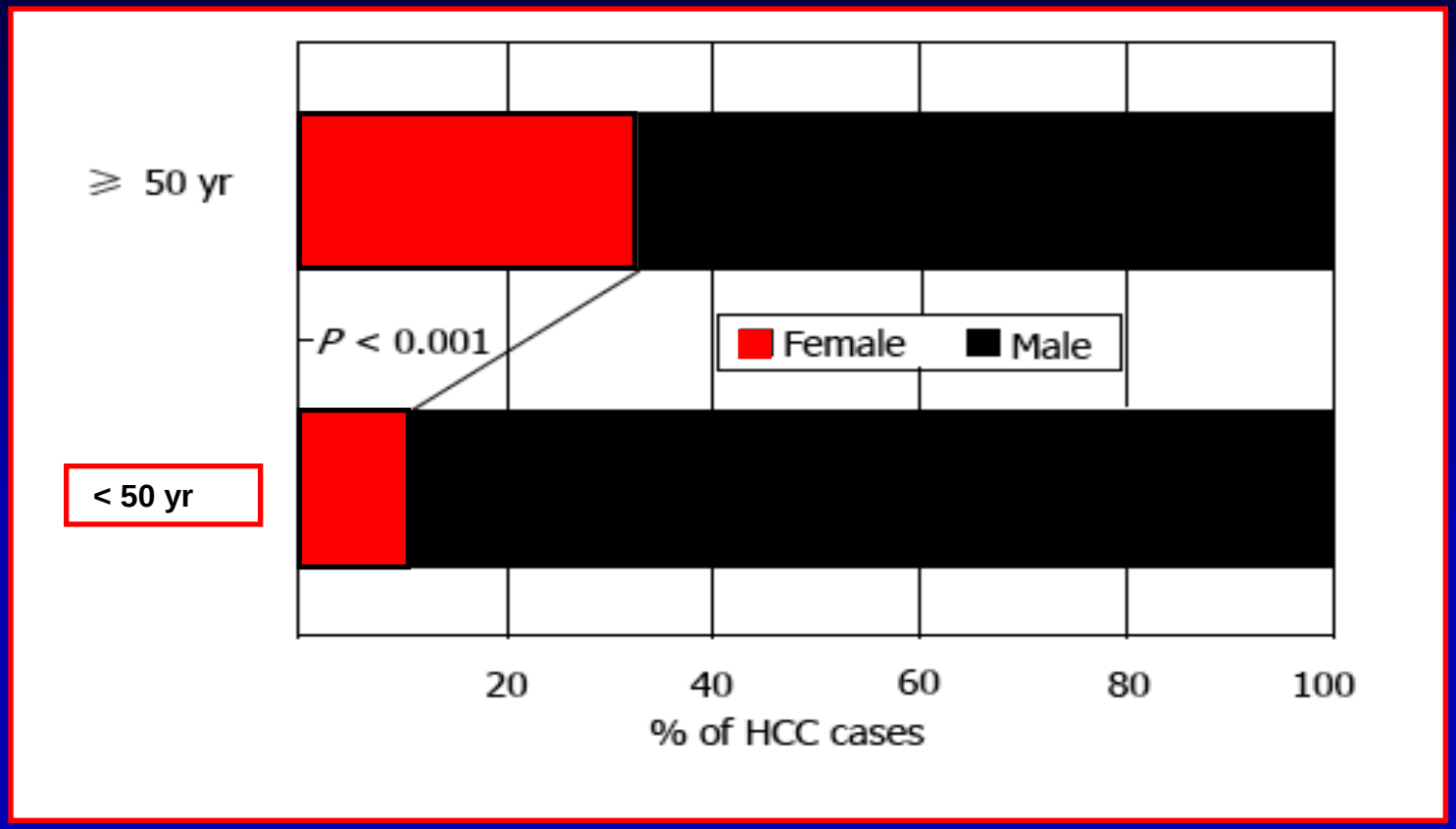
Reproductive status and HCC risk in women with chronic viral hepatitis

218 women HCC (majority **infected with HBV or HCV**), 719 controls

Reproductive factor	HCC OR (95% CI)	P value
# full-time pregnancies (≥4 vs ≤1)	0.45 (0.24-0.84)	0.0216
Older age of natural menopause (≥50, 45-49, ≤45 yrs respectively)	1.46 (0.52-4.08) 2.14 (0.80-5.73) 4.27 (1.01-18.07)	0.0251
Bilateral oophorectomy <age 50 yrs	2.57 (1.42-4.63)	0.0003

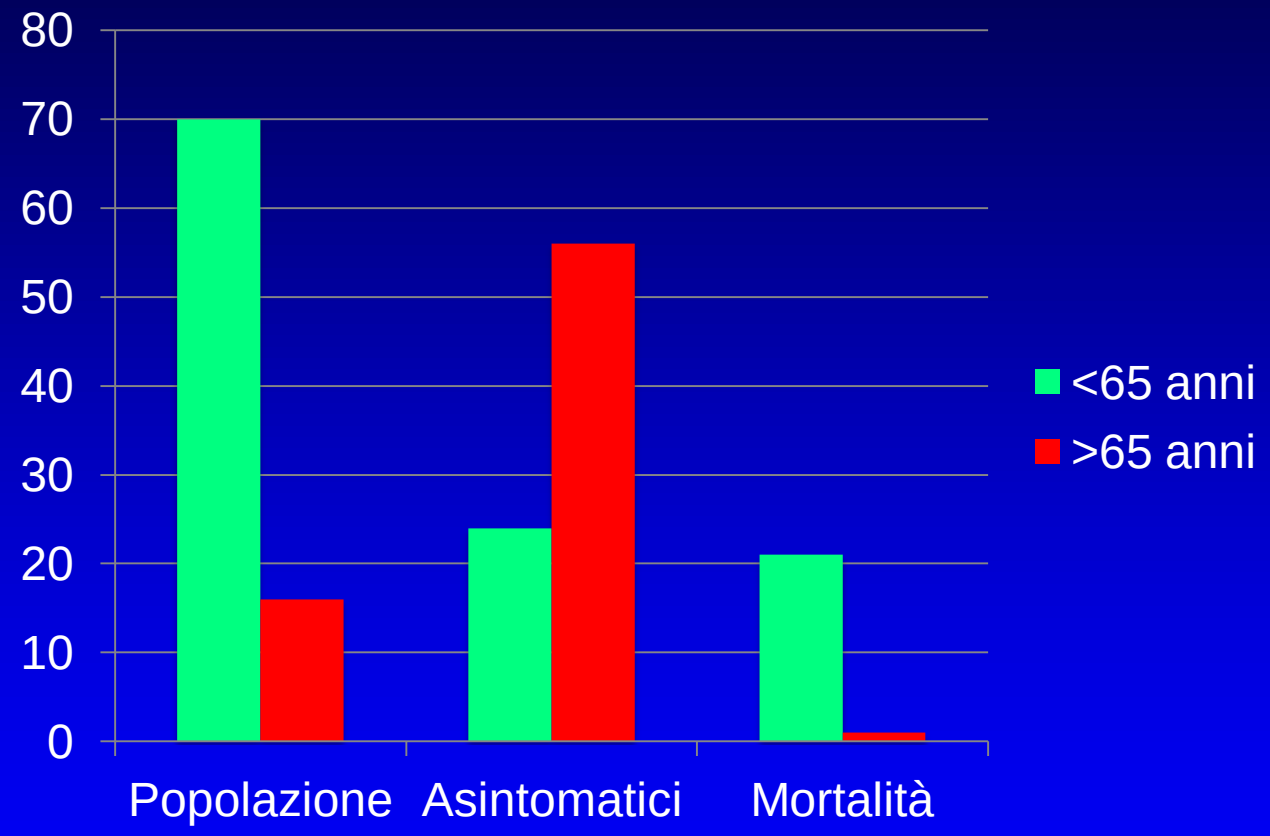
Yu MW et al, Hepatology 2003

Comparison of male-to-female ratio between two age groups of HBV-related HCC patients without HCV infection.



Shimizu, 2007

CBP alla presentazione



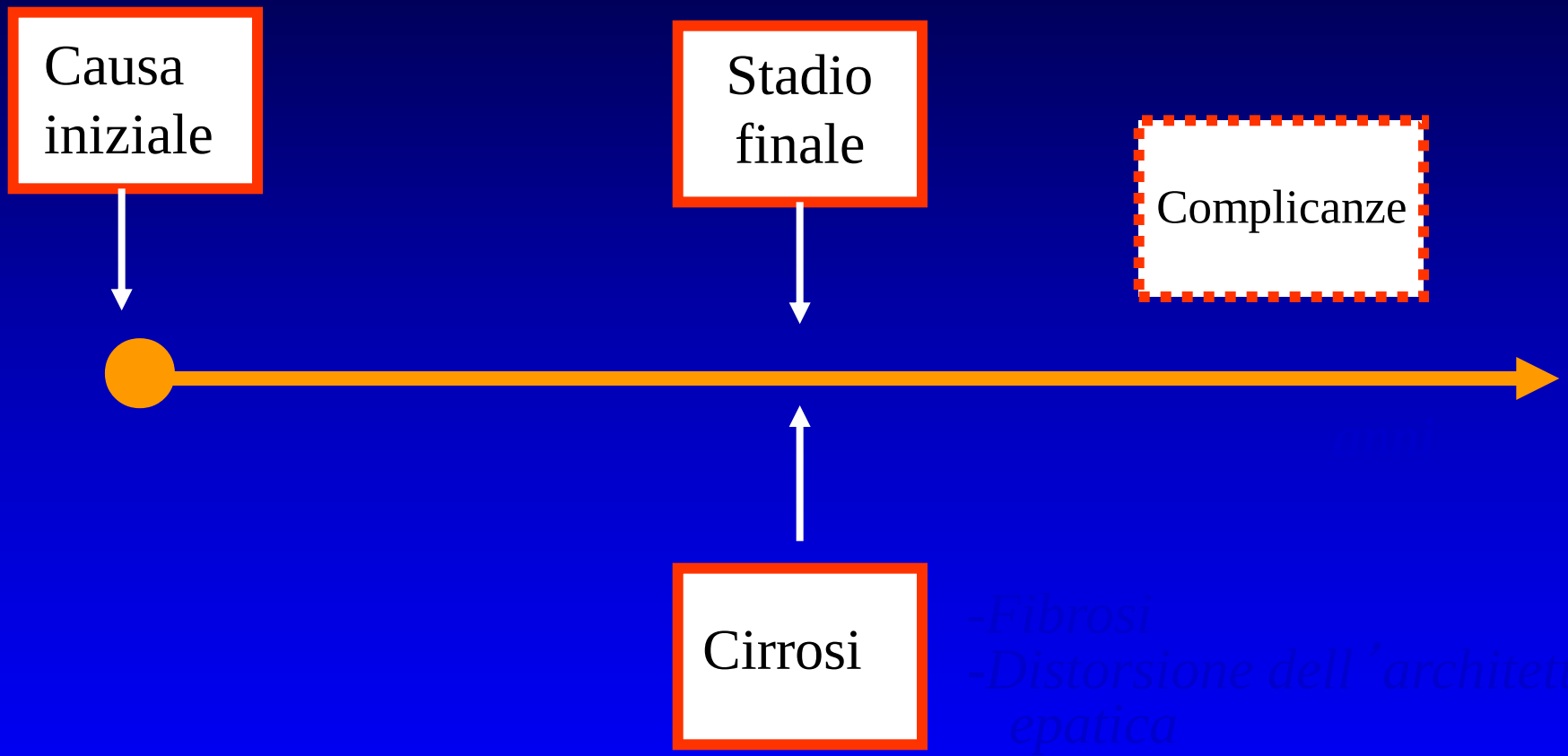
Floreani A, 1991

Invecchiamento ed epatopatie

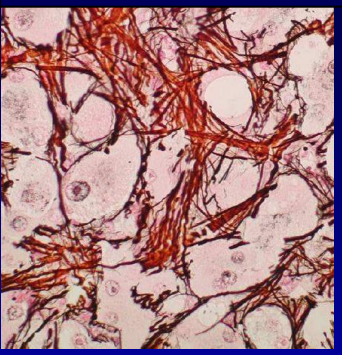
Effetto dell'invecchiamento

- sulla gravità del danno epatico
- sulla progressione della fibrosi
- sulla terapia

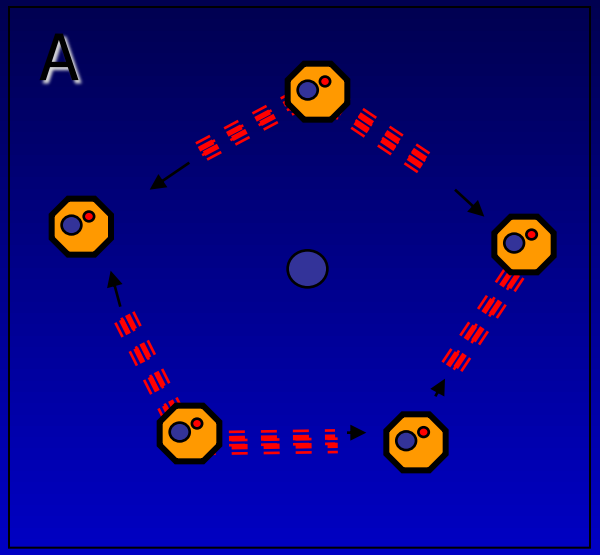
Storia naturale delle epatopatie

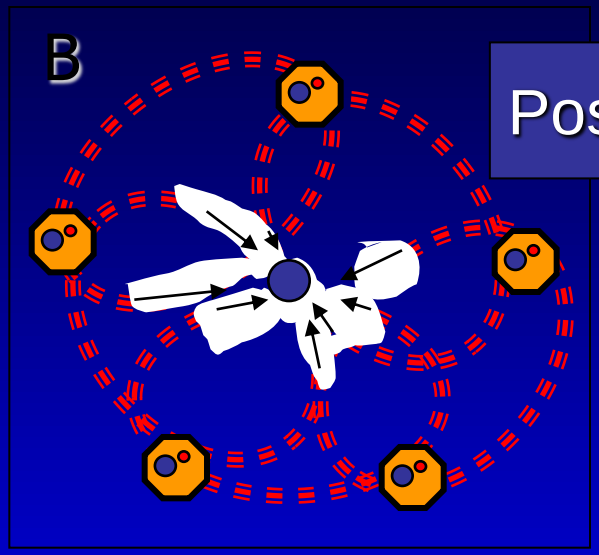


Patterns of hepatic fibrosis development

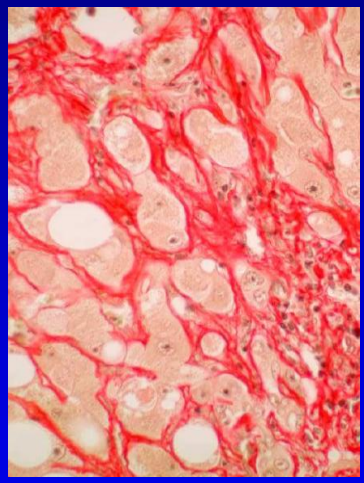


Biliary Type

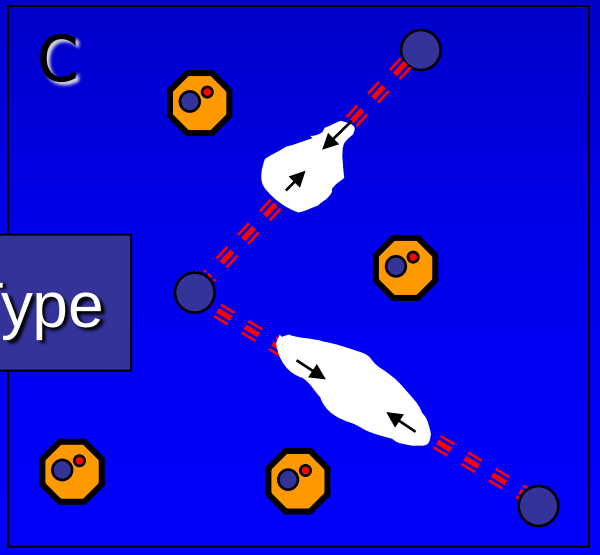


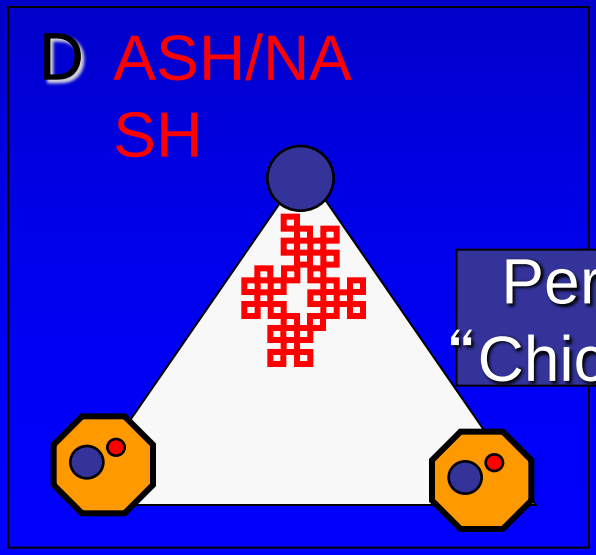


Post-necrotic



Vascular Type

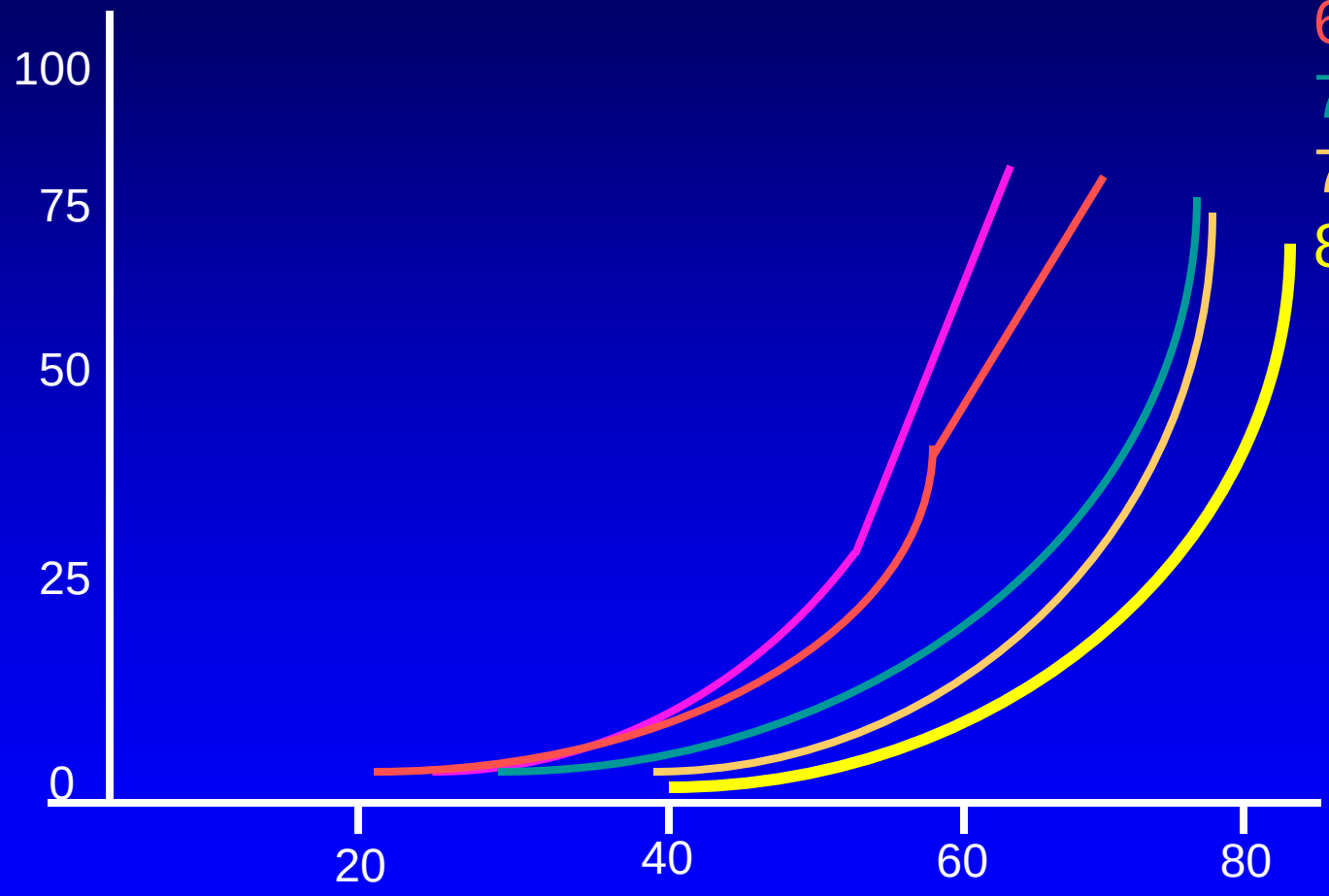




Pericellular
“Chicken Wire”

Pinzani M, and Rombouts K., Dig Liv Dis 2004; 36:231-242

Età in cui la probabilità di cirrosi è del 50%

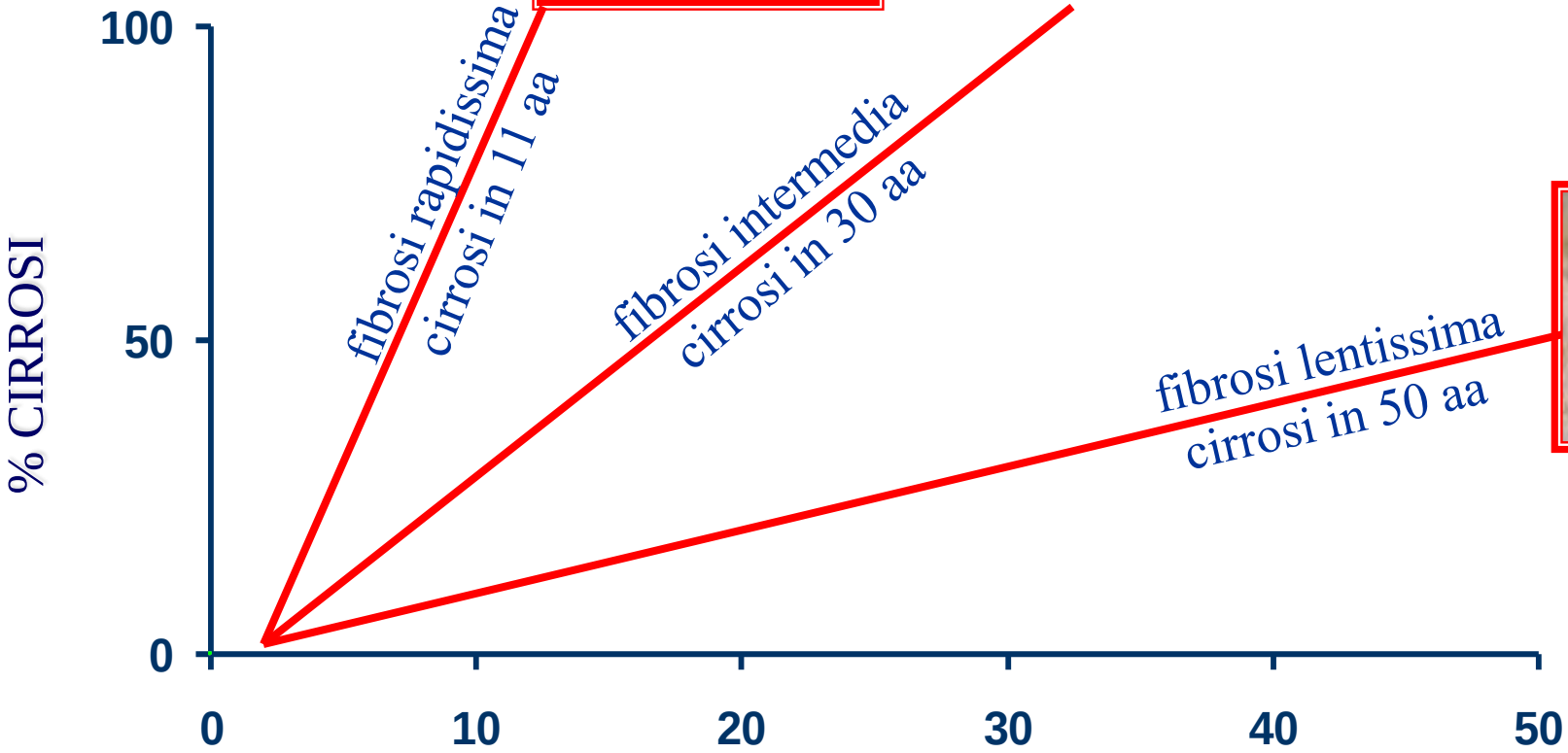


61 per ALD
65 per HBV
72 per HCV
74 per HG
81 per CBP

Poynard *T et al, J Hepatol 2003*

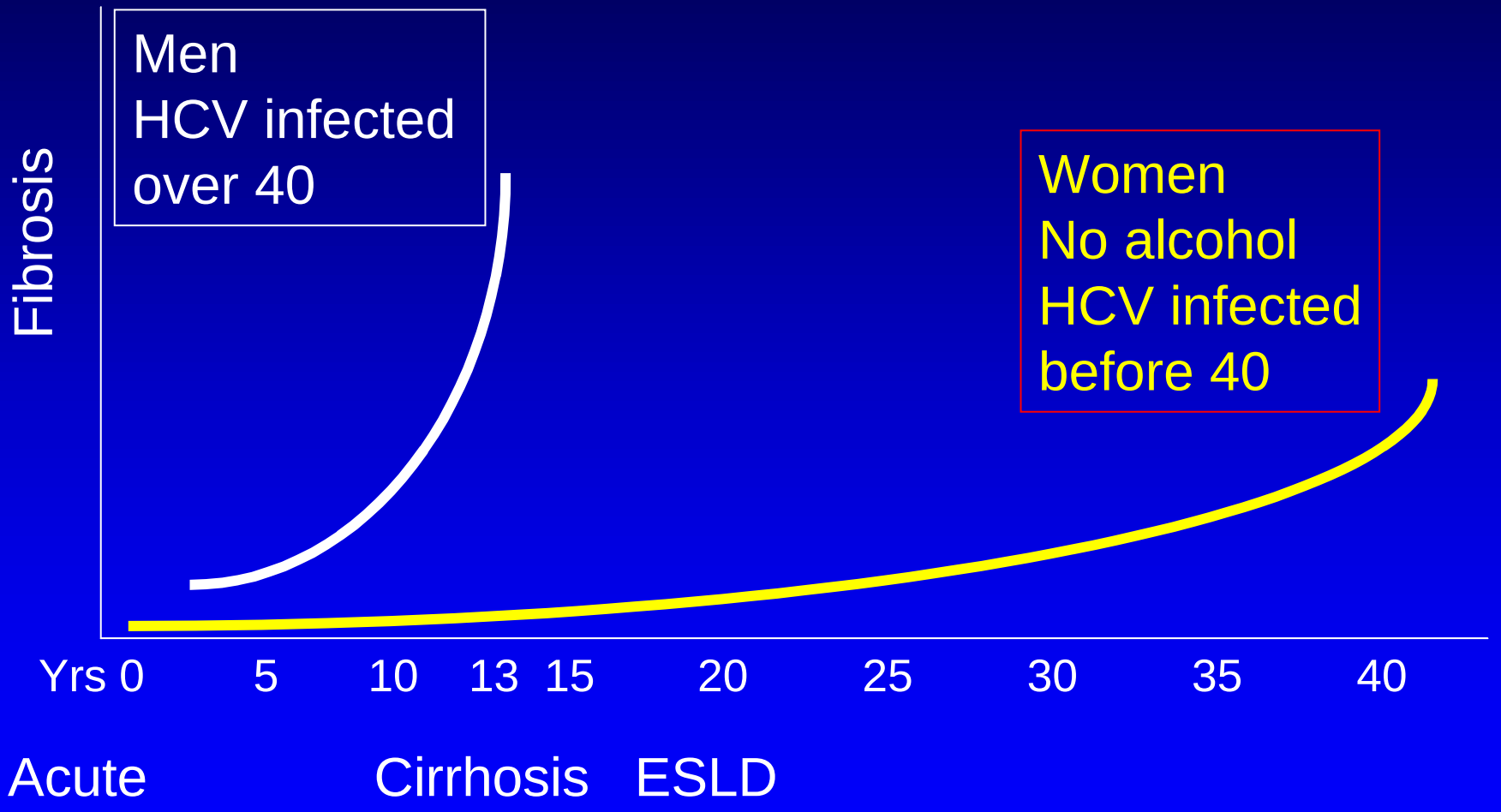
Epatite C come modello

Progressione della malattia



(Poynard et al Lancet 1997;349:825-832)

The natural history of chronic hepatitis C from Fibrosis to Cirrhosis

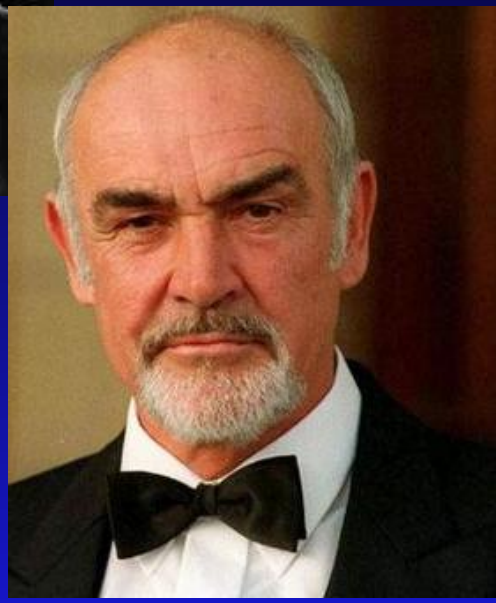


Poynard et al., Lancet 1997

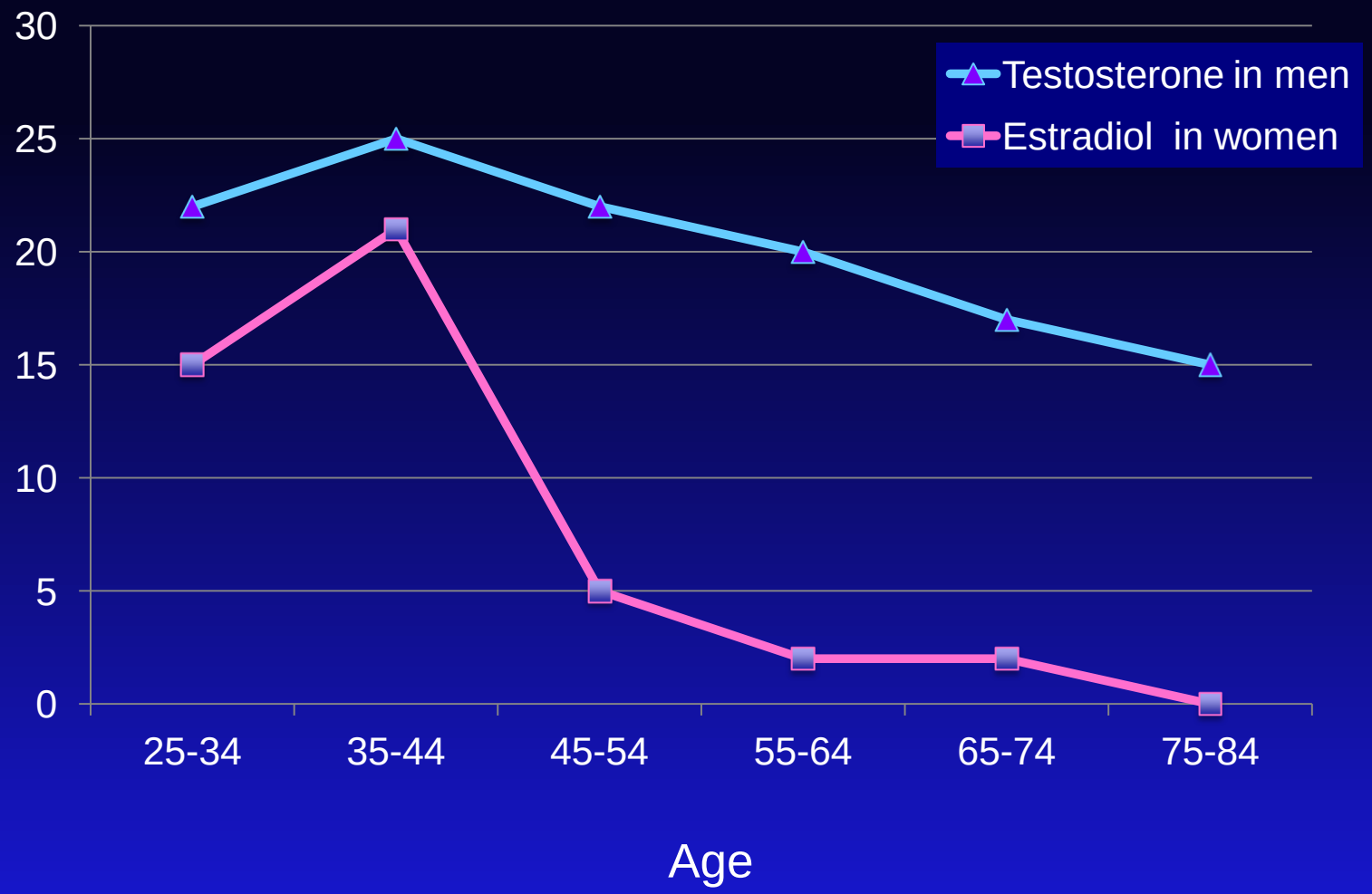
Madre Natura è …….

Brigitte Bardot

Sean Connery



Normal Testosterone and Estradiol levels throughout life (rough estimate)



Evidence of the presence of ER alfa in the liver

Characterization of estrogen receptor from human liver. Gastroenterology 1989

Ethanol-induced increase in cytosolic estrogen receptors in human male liver: a possible explanation for biochemical feminization in chronic liver disease due to alcohol. Hepatology1989

Type of estrogen receptor determines response to antiestrogen therapy. Cancer Research 1996

Variant liver estrogen receptor transcripts already occur at an early stage of chronic liver disease. Hepatology 1998

Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. Hepatology 1998

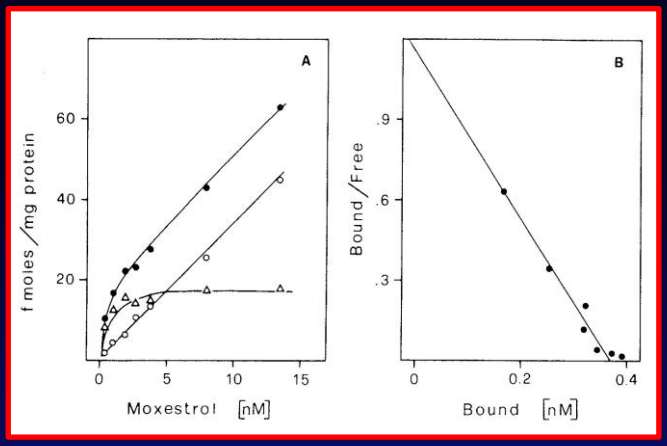
Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. Br J Cancer 2001

Phytoestrogens and liver disease. Mol Cell Endocrinol 2002

Estrogen receptor classification for hepatocellular carcinoma: comparison with clinical staging systems. JCO 2003

Characterization of Estrogen Receptor From Human Liver

GIAN PAOLO ROSSINI, GRAZIA MARIA BALDINI, ERICA VILLA, and FEDERICO MANENTI



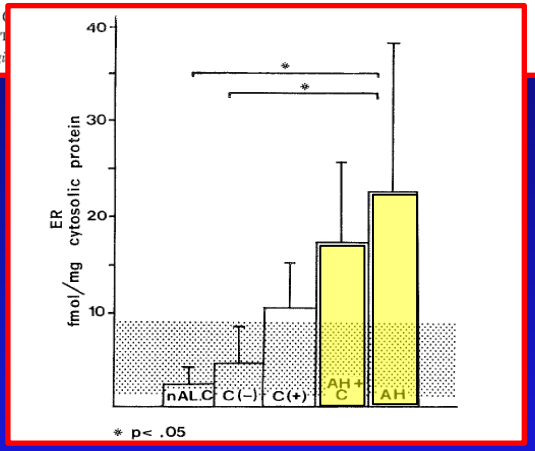
Gastroenterology 1989

Ethanol-Induced Increase in Cytosolic Estrogen Receptors in Human Male Liver: A Possible Explanation for Biochemical Feminization in Chronic Liver Disease Due to Alcohol

ERICA VILLA, GRAZIA M. BALDINI, ELISABETTA CARIANI, CRISTINA TA

Cattedra di Gastroenterologi

Hepatology 1988



Evidence of the presence of AR in the liver

Eagon PK, Elm MS, Stafford EA, Porter LE. Androgen receptor in human liver:
characterization and quantitation in normal and diseased liver. Hepatology. 1994
Jan;19(1):92-100

Eagon PK, Francavilla A, DiLeo A, et al. . Quantitation of estrogen and androgen receptors in HCC and adjacent normal human liver. Dig Dis Sci. 1991
Sep;36(9):1303-8.

Eagon PK, Porter LE, Francavilla A, DiLeo A, Van Thiel DH. Estrogen and androgen receptors in liver: their role in liver disease and regeneration. Semin
Liver Dis. 1985 Feb;5(1):59-69. Review.

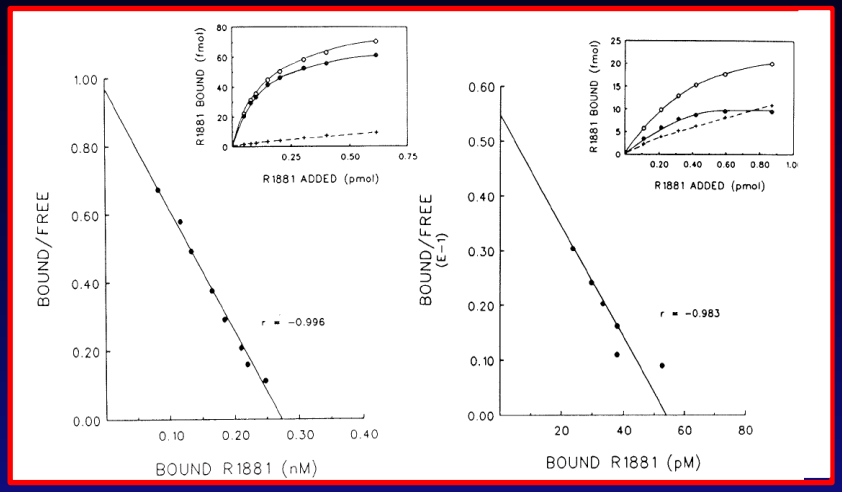
Li Z, Tuteja G, Schug J, Kaestner KH. Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer. Cell. 2012 Jan 20;148(1-2):72-83.

Zhu R, Zhang JS, Zhu YZ, Fan J, Mao Y, Chen Q, Zhu HG. HBx-induced androgen receptor expression in HBV-associated hepatocarcinoma is independent of the methylation status of its promoter. Histol Histopathol. 2011 Jan;26(1):23-35.

And many others……

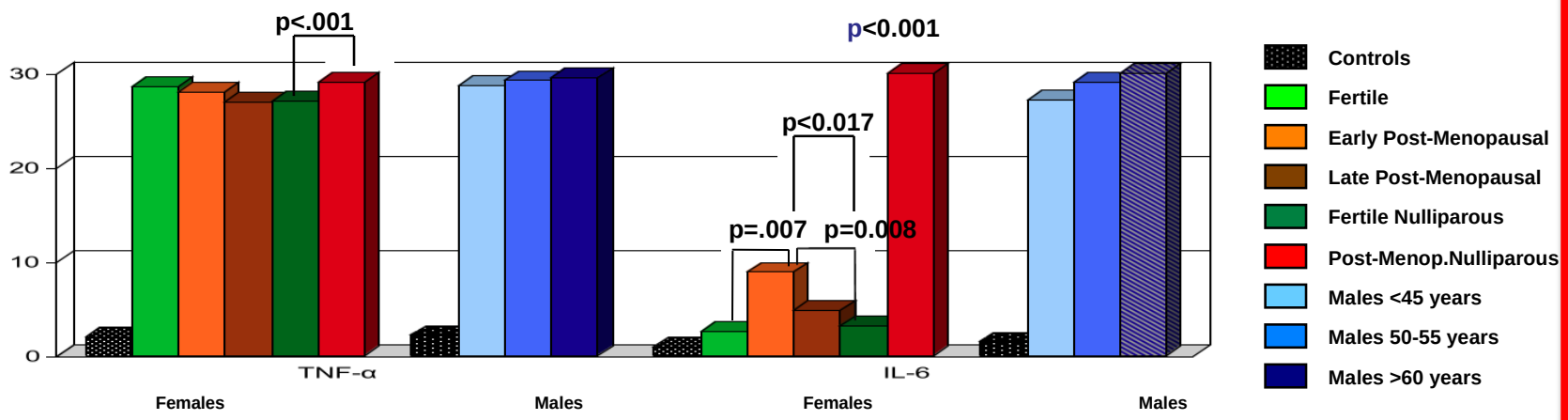
Androgen Receptor in Human Liver: Characterization and Quantitation in Normal and Diseased Liver

PATRICIA K. EAGON,[1, 2, 3] MARY S. ELM,[2] ELIZABETH A. STAFFORD[2*] AND LYNNE E. PORTER[2]



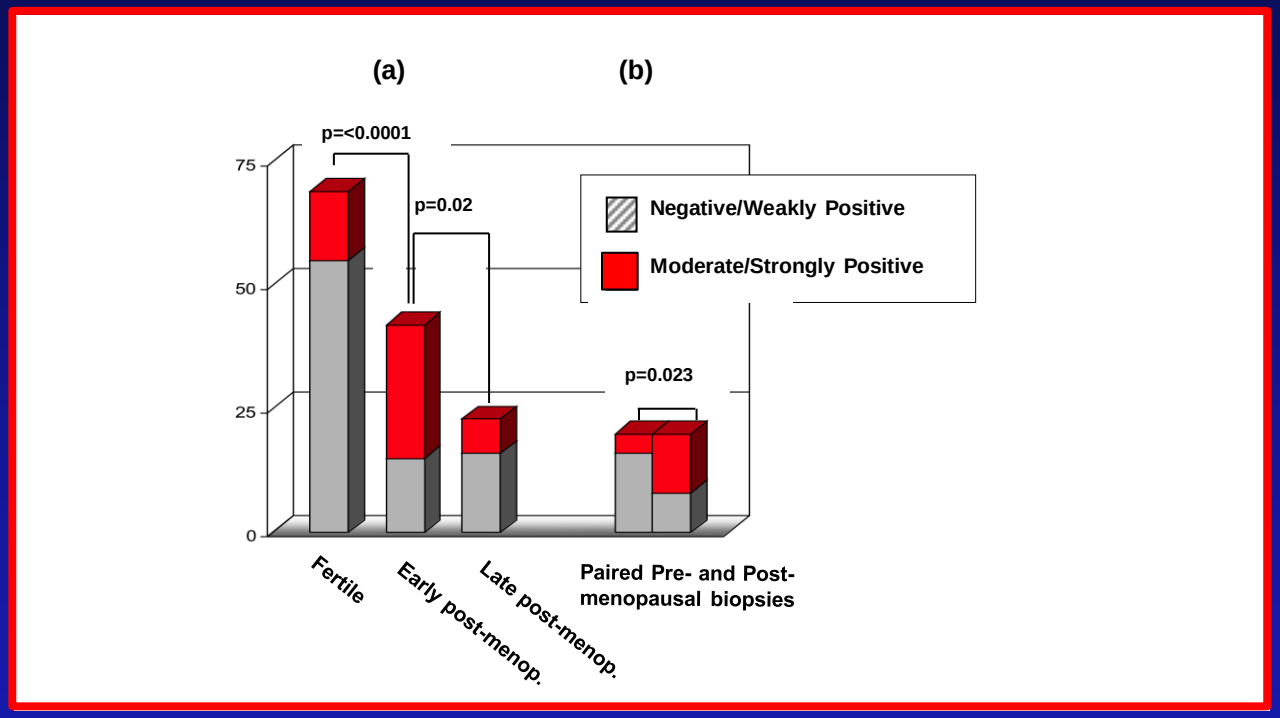
Hepatology 1994

TNF-alfa and IL-6 levels in fertile and post-menopausal HCV+ women compared with males stratified by age groups according to females reproductive status.



Villa et al. *Gastroenterology* 2011

TNF-α expression in the liver



Villa et al., Gastro 2011

OPEN ACCESS Freely available online

PLOS ONE

Reproductive Status Is Associated with the Severity of Fibrosis in Women with Hepatitis C

Erica Villa[1¶]*, Ranka Vukotic[1¶], Calogero Cammà[2], Salvatore Petta[2], Alfredo Di Leo[3], Stefano Gitto[1], Elena Turola[1¶], Aimilia Karampatou[1¶], Luisa Losi[4¶], Veronica Bernabucci[1¶], Annamaria Cenci[5], Simonetta Tagliavini[5], Enrica Baraldi[5], Nicola De Maria[1], Roberta Gelmini[6], Elena Bertolini[1¶], Maria Rendina[3¶], Antonio Francavilla[7]

September 2012 | Volume 7 | Issue 9 | e44624

Four groups of women selected according to timing of reproductive phases

- Full reproductive (n. 123): i.e. women with regular menses and <45 years of age)
- Pre-menopausal (n. 38): women included in this group were those who entered menopause 3 to 5 years after enrolment in the study.
- Early menopausal (n. 50): included in this group were women menopausal from not more than 5 years from enrolment;
- Late menopausal (n. 144): women that were menopausal since at least 10 years.

Univariate and multivariate analysis for fibrosis in the whole cohort of patients with chronic hepatitis C.

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex*	0.406 (0.254–0.649)	0.000	0.460 (0.236–0.896)	0.023
Age (years)	1.049 (1.027–1.072)	0.000	1.031 (1.000–1.062)	0.050
Duration of HCV infection (years)	1.064 (1.023–1.107)	0.002	0.989 (0.941–1.039)	0.654
Necro-inflammation	1.427 (1.312–1.553)	0.000	1.401 (1.239–1.584)	0.0001
Steatosis (0 *vs.* >20%)	1.469 (1.062–2.032)	0.020	1.301 (0.840–2.016)	0.239
Circulating Estradiol (pg/ml)	0.982 (0.972–0.991)	0.000	0.980 (0.962–0.999)	0.040
Blood Iron (ng/mL)	1.010 (1.003–1.017)	0.006	1.018 (0.993–1.043)	0.170
Ferritin (ng/mL)	1.002 (1.000–1.003)	0.031	1.001 (0.995–1.006)	0.784
ALT (IU/L)	1.008 (1.005.011)	0.000	1.002 (0.998–1.006)	0.279
GGT (IU/L)	1.016 (1.010–1021)	0.000	1.003 (0.996–1.010)	0.387
Platelet count ($x10^3/mm^3$)	0.973 (0.967–0.979)	0.000	0.974 (0.967–0.981)	0.0001
Portal vein diameter (mm)	2.233 (1.901–2.622)	0.000	1.903 (0.539–2.354)	0.000

*Male as reference. HCV, hepatitis C virus; BMI, body mass index; ALT, alanine aminotransferase; GGT, c-glutamyl transpeptidase; OR, odds ratio; CI, confidence interval

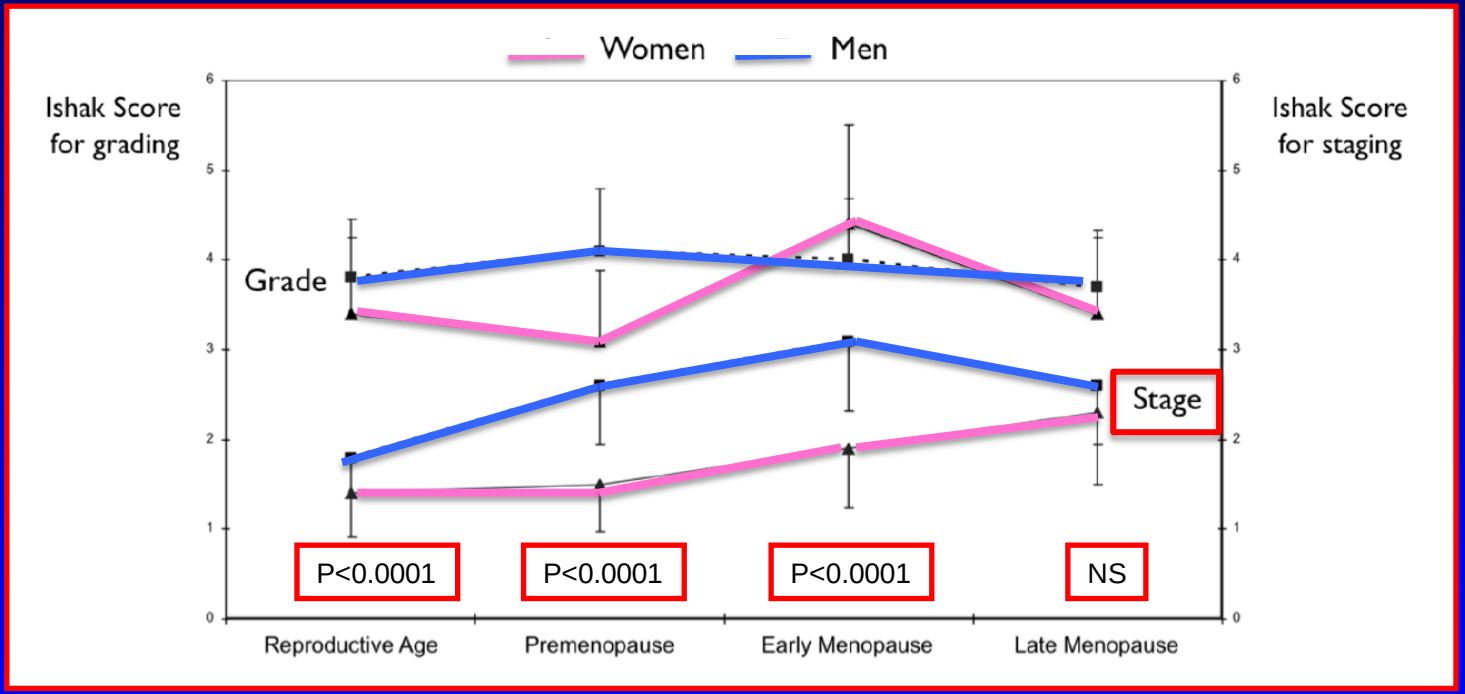
Villa et al, PlosOne 2012

Univariate and multivariate analysis for fibrosis in the women with chronic hepatitis C

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.089 (1.040–1.140)	0.000	1.028 (0.939–1.126)	0.553
Duration of HCV infection (years)	1.118 (1.037–1.205)	0.004	1.015 (0.884–1.166)	0.833
HCV infection's Acquisition Age	1.036 (1.015–1.057)	0.001	1.000 (0.879–1.139)	0.996
Necro-inflammation	1.458 (1.277–1.665)	0.000	1.506 (1.181–1.1.922)	0.001
Steatosis (0 *vs.* >20%)	1.775 (1.018–3.095)	0.043	3.029 (1.154–7.951)	0.024
Circulating Estradiol (pgml)	0.977 (0.963–0.991)	0.001	0.973 (0.947–0.999)	0.041
Baseline HCV RNA (IU/mL)	1.000 (1.000–1.000)	0.024	1.000 (1.000–1.000)	0.578
ALT (IU/L)	1.009 (1.004–1.013)	0.000	1.011 (0.003–1.019)	0.009
GGT (IU/L)	1.028 (1.016–1039)	0.000	1.008 (0.992–1.025)	0.327
Platelet count ($\times 10^3/mm^3$)	0.970 (0.969–0.981)	0.000	0.988 (0.974–1.002)	0.099
Portal vein diameter (mm)	2.392 (1.804–3.171)	0.000	2.644 (1.657–4.220)	0.0001

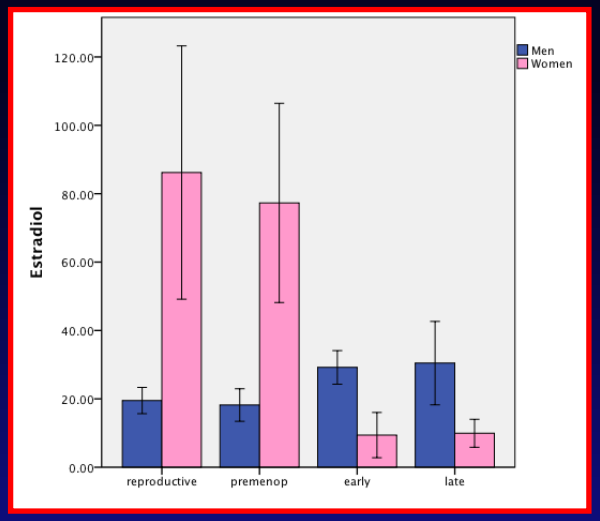
Villa et al, PlosOne 2012

Mean necro-inflammation and fibrosis scores in the 4 sub-groups of female and age-matched male patients with chronic hepatitis

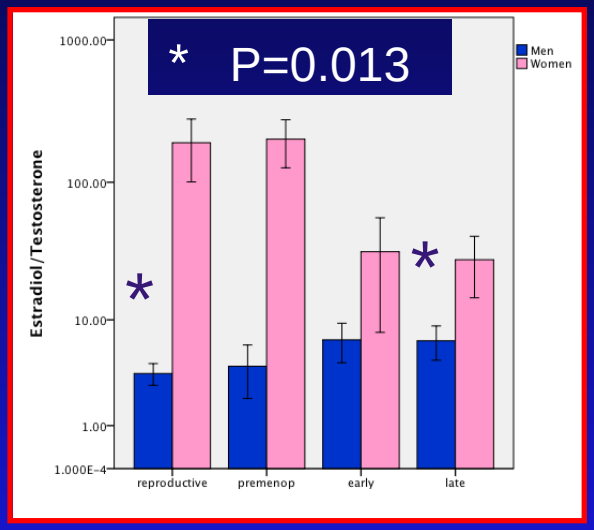


Villa et al, PlosOne 2012

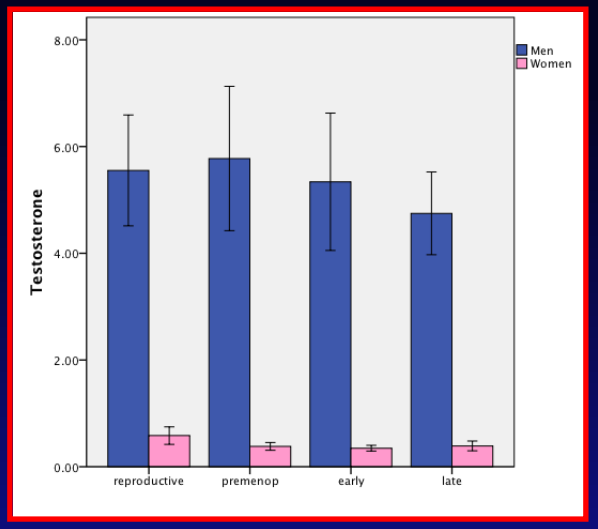
Estradiol and Testosterone serum levels and E2/T ratio in men and women divided according to women's reproductive phases



Estradiol



E2/T Ratio



Testosterone

Villa et al, PlosOne 2012

Invecchiamento ed epatopatie

Effetto dell'invecchiamento

- sulla gravità del danno epatico
- sulla progressione della fibrosi
- sulla terapia

I Pazienti anziani sono candidati scarsi per la terapia con PEG-IFN+Riba nel trattamento dell'epatite cronica C?

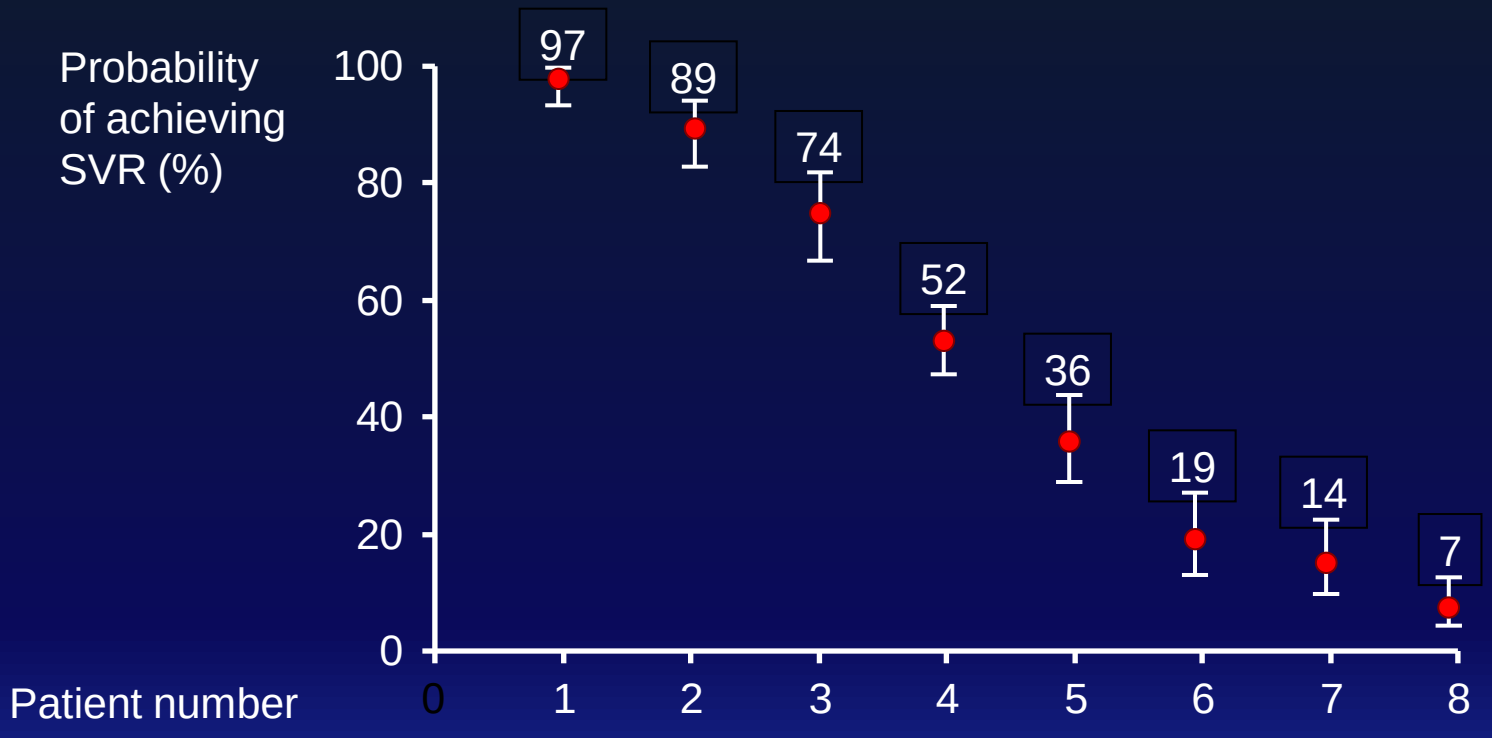
Table 1. Response to Viral Therapy

Response	Elderly n (%)	Younger Adult n (%)	*P*-value
Early virological response	18 (54.5)	53 (80.3)	.002
No response	7 (21.2)	3 (4.5)	.001
Virological response (end of treatment)	18 (54.5)	55 (83.3)	.002
Relapse	3 (9.1)	9 (13.6)	*
Sustained virological response	15 (45.5)	46 (69.7)	.02

*Not significant.

Floreani A. et al JAGS 2006

HCV genotype 1: Probability of SVR based on interaction of multiple factors



Cirrhosis	**No**	No	No	No	No	No	No	**Yes**
ALT quotient	**7**	2	2	2	2	2	1	**1**
Age (years)	**20**	20	43	43	43	60	60	**60**
BMI (kg/m^2)	**20**	20	26	26	26	30	30	**30**
HCV RNA (IU/mL $\times$ 10^3)	**40**	40	40	1200	9000	9000	9000	**9000**

Foster GR, et al. Scand J Gastroenterol 2007;42:247-255

% of SVR in males and females of different age groups

Author	Patients n. (M/F ratio)	Type of IFN used	Menopausal status	Age	% SVR
Hayashi, 1998	311 (199/112)	Lymphoblastoid IFN	Not known	<40 years	Females: 75% Males 33%
				>40 years	Females : 15% Males 25%
Elefsiniotis, 2008	185 (74/44)	PEG 2b/Riba	Not known	<35 years 35-55 years > 55 years	Whole group 88.7% NR NR
Sezaki, 2009	490* (179/121)	PEG 2b/Riba	Not known	<50 years	Females: 52% Males 65%
				>50 years	Females : 22% Males: 53%
Reddy, 2009	569* (438/131)	PEG 2a/Riba	Not known	< 50years > 50years	Whole group 52% (29% females) 39% (40% females)

NR: non reported; * only genotype 1; ** median age

GASTROENTEROLOGY 2011;140:818–829

Early Menopause Is Associated With Lack of Response to Antiviral Therapy in Women With Chronic Hepatitis C

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Baseline Demographic, Laboratory, Metabolic and Histological Features of 1000 Patients with Chronic Hepatitis C According to Gender

Variables	Men (n=558)	Women (n=442)	p
Mean Age at enrolment - years	**47.9±11.6**	51.9±11.3	<.001
Mean Body Mass Index – Kg/m^2	**26.3±3.6**	24.7±3.8	<.001
Platelets count X 10^3/mm^3	**179.0±56.5**	203.4±66.5	<.001
Alanine Aminotransferase – IU/L	**98.6±87.4**	73.4±67.4	<.001
GGT – IU/L	**57.1±52.4**	37.1±37.3	<.001
Insulin – µU/mL	6.1±3.5	10.0±6.4	.093
HOMA-score	1.5±0.7	2.6±2.2	.124
Length of HCV infection (years)	14,1 ±1.6	13,5 ±2.2	.073
Histology at Biopsy			
Steatosis:			
<5%	328 (63.1)	261 (63.5)	.95
≥5% to <20%	150 (28.8)	116 (28.2)	.99
≥20%	42 (8.0)	34 (8.2)	.99
Grade of Inflammation			
0-5	391 (71.89)	332 (80.2)	
6-11	128 (24.5)	74 (17.9)	.018
12-18	4 (0.8)	8 (1.9)	
Stage of Fibrosis			
0-3	**443 (84.4)**	372 (80.6)	
4-6	82 (15.6)	43 (10.4)	.020
Cirrhosis	**69 (12.3)**	30 (6.7)	.003

Villa et al., Gastro 2011

Menopause	2.436 (1.620-3.662)	<.001	1.802 (1.154-2.813)	.01
Length of Estrogen deprivation -y				
<5 years	2.497 (1-010-8.172)	.047	8.055 (1.834-25.390)	.006
5-10 years	1.295 (0.497-3.375)	.597	1.683 (0.335-8.458)	.527
≥10 years	2.374 (1.137-4.354)	.021	4.277 (0.747-24.503)	.103
GGT - IU/L	1.017 (1.008-1.026)	<.0001	2.165 (1.364-3.436)	.001
Cholesterol – mg/dL	0.992 (0.983-1.001)	.074	0.967 (0.943-0.991)	.008
HCV Genotype				
1-4 vs 2-3	3.690 (2.427-5.617)	.000	3.861 (2.433-6.134)	.006
Histology at Biopsy				
Steatosis	1.402 (0.940-2.091)	.097	3.053 (0.925-10.076)	.067
Grade of Inflammation	1.131 (1.045-1.225)	.002	0.977 (0.748-1.276)	.863
Stage of Fibrosis	1.494 (1.246-1.793)	<.0001	0.614 (0.299-1.299)	.183
Cirrhosis	0.823 (0.206-3.292)	.783		

Villa E et al., Gastro 2011

Univariate and Multivariate Logistic Regression Analysis of Risk Factors for SVR Failure in 442 Female Patients with Chronic Hepatitis C

Menopause	2.436 (1.620-3.662)	<.001	1.802 (1.154-2.813)	.01
Length of Estrogen				

Women with Genotype 1 HCV Infections (n=252)				
Menopause	3.625 (1.562-5.699)	.003	2.908 (1.544-5.478)	.001

Steatosis	1.402 (0.940-2.091)	.097	3.053 (0.925-10.076)	.067
Grade of Inflammation	1.131 (1.045-1.225)	.002	0.977 (0.748-1.276)	.863
Stage of Fibrosis	1.494 (1.246-1.793)	<.0001	0.614 (0.299-1.299)	.183
Cirrhosis	0.823 (0.206-3.292)	.783		

Villa E et al., Gastro 2011

JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2012 doi:10.1111/j.1365-2893.2012.01593.x

Peginterferon-A_2B plus ribavirin is more effective than peginterferon-A_2A plus ribavirin in menopausal women with chronic hepatitis C

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Factors independently associated with SVR by multivariate analysis

Women

Lower hepatic steatosis	0.028
Absence of menopause	0.001
Genotype 2 HCV infection	<0.0001
Use of Peg-IFNα-2b	0.002

Men

Lower GGT	0.001
Genotype 2 HCV infection	<0.0001

Villa et al., J Viral hepatitis 2012

Efficacy of treatment according to Pegylated interferon used in the whole cohort and in men and women (stratified by reproductive status)

Variable	ETR (%)	p	SVR (%)	P
Whole cohort (746)				
PEG IFN 2a (345)	225 (65.2)	0.001	155 (44.9)	0.139
PEG IFN 2b (401)	221 (55.1)		197 (49.1)	
Men (431)				
PEG IFN 2a (202)	132 (65.3)	0.005	99 (46.5)	0.489
PEG IFN 2b (229)	119 (52.0)		116 (43.2)	
Women (315)				
PEG IFN 2a (143)	93 (65.0)	0.297	56 (39.2)	**0.007**
PEG IFN 2b (171)	102 (59.6)		**93 (54.4)**	
Women of reproductive age (124)				
PEG IFN 2a (65)	48 (73.4)	0.903	35 (53.8)	**0.055**
PEG IFN 2b (59)	43 (72.9)		**41 (70.7)**	
Menopausal women (191)				
PEG IFN 2a (78)	45 (57.7)	0.455	21 (26.9)	**0.008**
PEG IFN 2b (113)	59 (52.2)		**52 (46.0)**	

Villa et al., J Viral hepatitis 2012

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WomenInHepatology
GENDER-C Project

Courtesy of Anne Shreivogl

Danno epatico da farmaci nell'anziano

MULTIFATTORIALE:

- Riduzione dei sistemi enzimatici (citocromo P450)
- Riduzione della coniugazione
- Alterazioni morfologiche del fegato senile
- Insufficienza renale (aumento della vita media e della biodisponibilità)