Solving the dilemma of anti-HCV therapy in HCV patients with normal ALT

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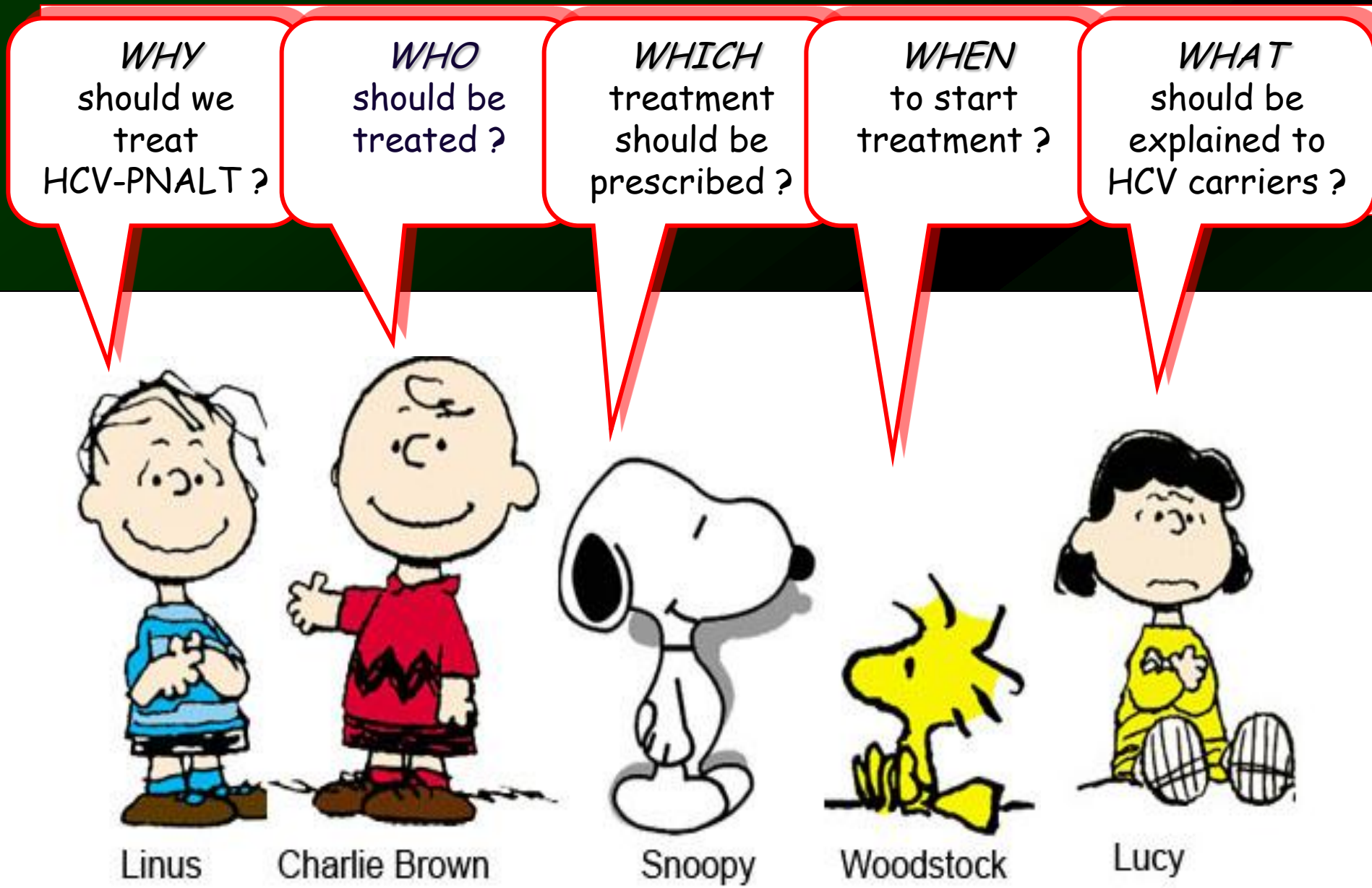

WHY should we treat HCV-PNALT ?
WHO should be treated ?
WHICH treatment should be prescribed ?
WHEN to start treatment ?
WHAT should be explained to HCV carriers ?
Linus
Charlie Brown
Snoopy
Woodstock
Lucy

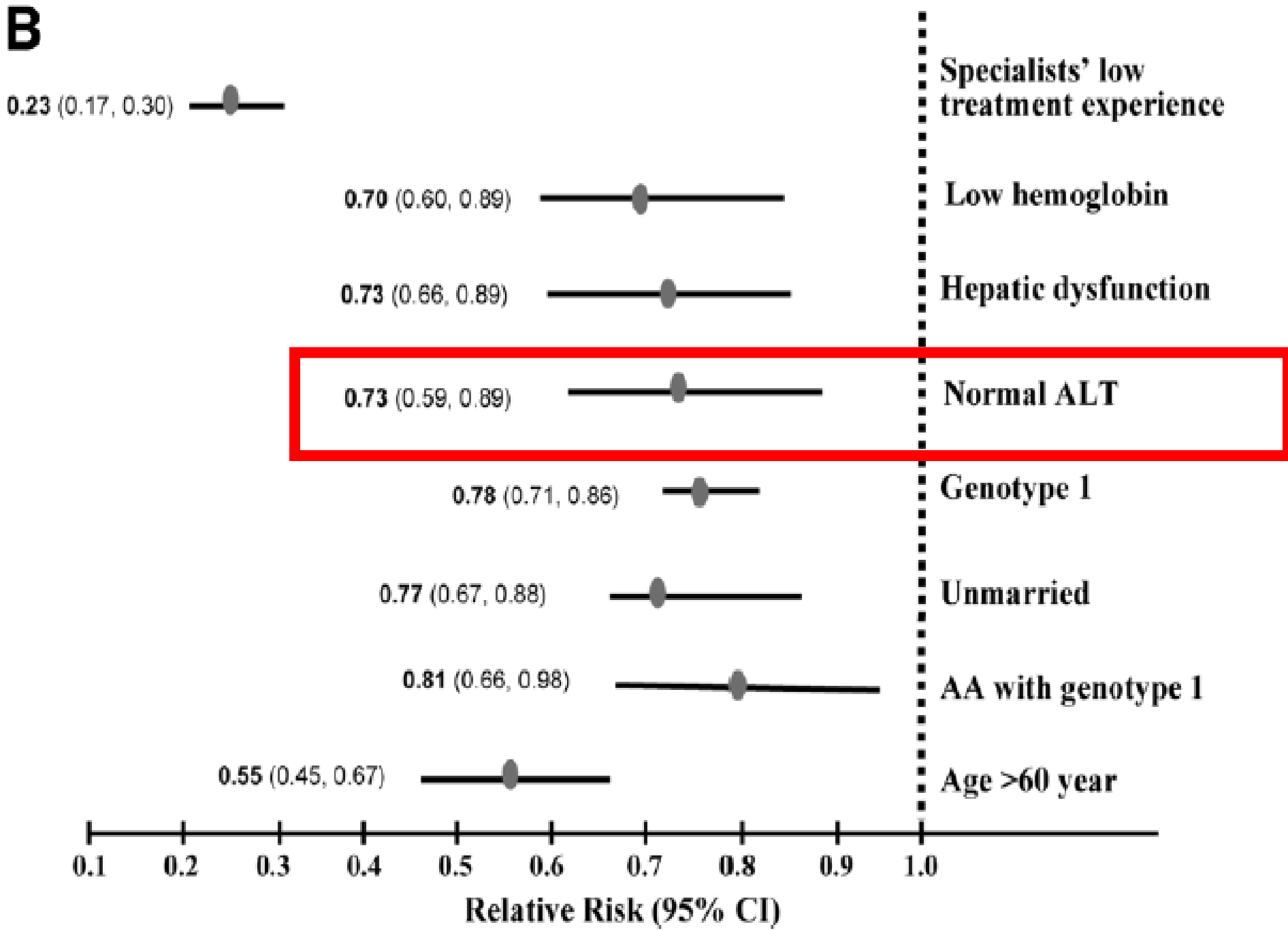
Patients with PNALT should not be treated

(NIH Consensus Conference, 1997; EASL Consensus Conference, 1999)

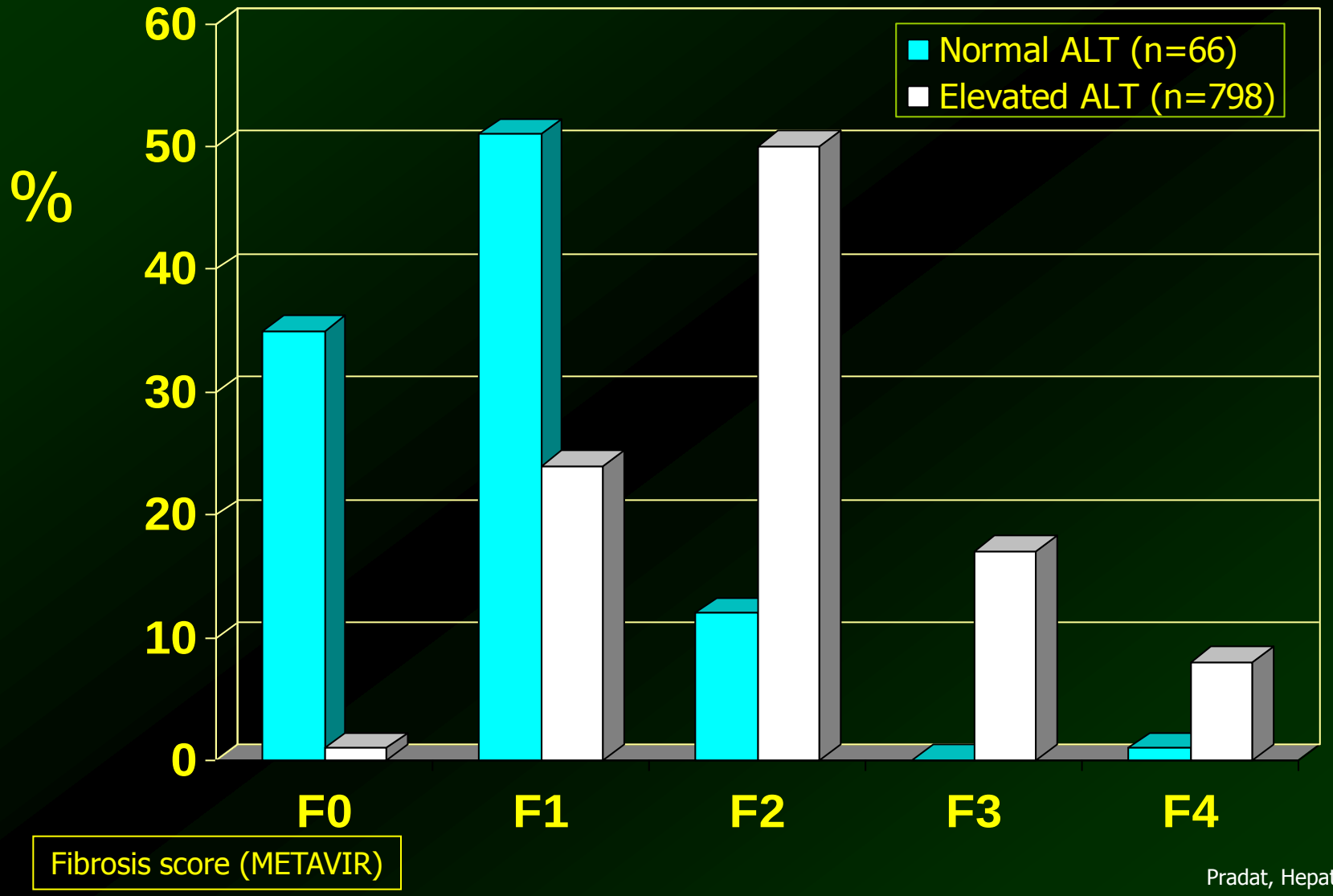
At present, it is NOT recommended that HCV carriers with PNALT undergo therapy in clinical practice because of :

1. Normal liver or mild disease in the majority of them
2. Low risk of progression
3. Uncertain response to therapy (SVR < 20%)
4. IFN-related worsening of liver disease (ALT flares) in up to 50% of the cases

Thus, these people should be followed up every 4-6 months or entered clinical trials.


B
0.23 (0.17, 0.30)
Specialists' low treatment experience
0.70 (0.60, 0.89)
Low hemoglobin
0.73 (0.66, 0.89)
Hepatic dysfunction
0.73 (0.59, 0.89)
Normal ALT
0.78 (0.71, 0.86)
Genotype 1
0.77 (0.67, 0.88)
Unmarried
0.81 (0.66, 0.98)
AA with genotype 1
0.55 (0.45, 0.67)
Age >60 year
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Relative Risk (95% CI)

Fibrosis in HCV carriers with PNAL and in patients with abnormal ALT values

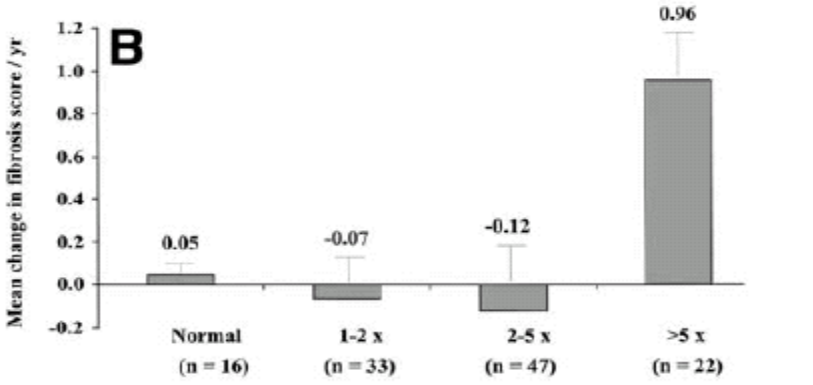


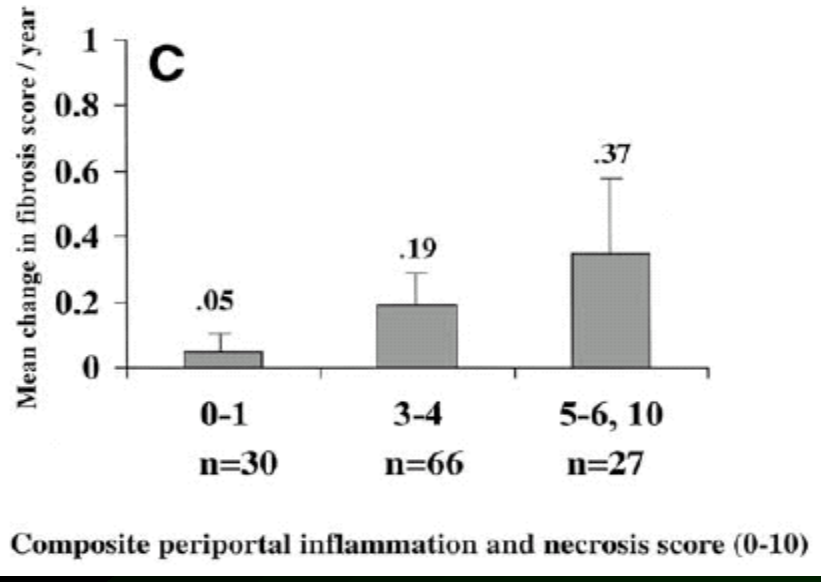
Pradat, Hepatology 2002

Progression of Fibrosis in Chronic Hepatitis C

GASTROENTEROLOGY 2003;124:97–104

MARC G. GHANY,* DAVID E. KLEINER,† HARVEY ALTER,§ EDWARD DOO,* FAROOQ KHOKAR,* KITTICHAI PROMRAT,* DAVID HERION,* YOON PARK,* T. JAKE LIANG,* and JAY H. HOOFNAGLE*





Conclusions: The best predictors of fibrosis progression in CHC are the extent of serum aminotransferase elevations and the degree of hepatocellular necrosis and inflammation on liver biopsy. These findings support the recommendation that patients with normal aminotransferase levels and mild liver histology can safely defer treatment.

Progression of Fibrosis in Chronic Hepatitis C

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ELSEVIER

Journal of Hepatology 38 (2003) 529–532

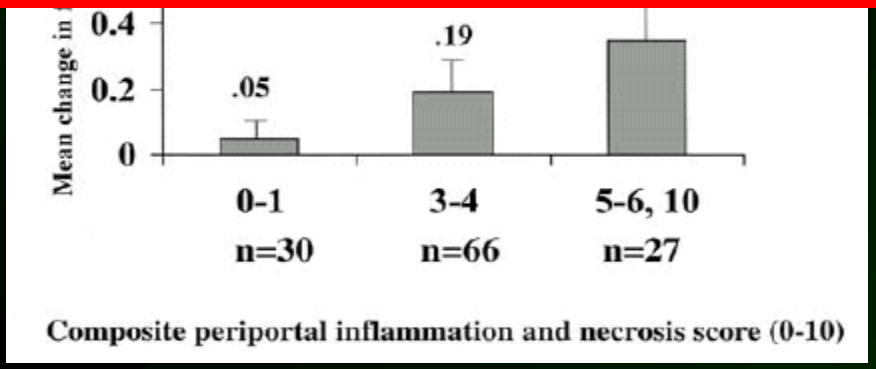
Journal of Hepatology

www.elsevier.com/locate/jhep

Editorial

HCV carriers with persistently normal aminotransferase levels: *normal* does not always mean *healthy*

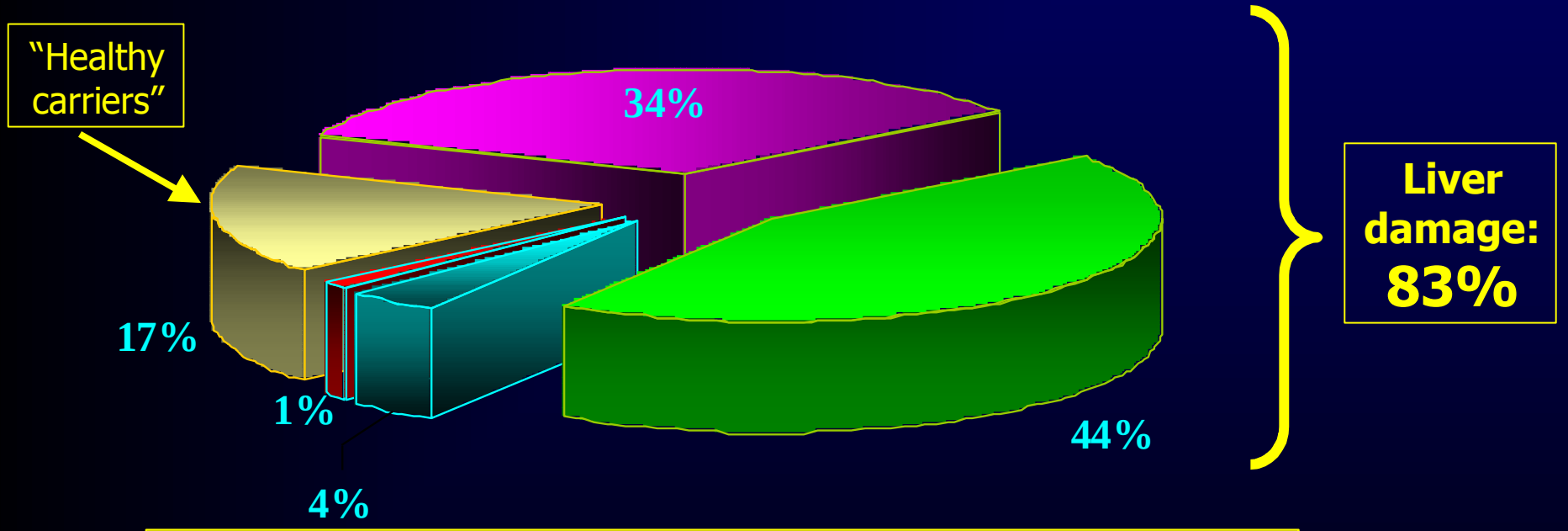
Claudio Puoti*



Liver Histology among 159 HCV carriers with PNAL

The Italian Study of the Asymptomatic C Carrier (ISACC)

PNAL = 9 normal values / 18 months



Puoti et al, J Hepatol 2002

ALT Flare in HCV Carriers with Initially (≥ 6 mo) Normal ALT

Author	N° cases	FU (yrs)	% ALT flare
Persico et al, 2000	37	4.1	23 %
Martinot-Peignoux et al, 2001	24	3.5	21 %
Tsuy et al, 2001	120	3.6	23.3 %
Puoti et al, 2002	880	1.8	21.5 %
Hui et al, 2003	40	6.3	27.5 %
Boccato et al, 2004	45	7.3	33 %
Rumi et al, 2005	206	1.5	18.4%

Is fibrosis in HCV Carriers with PNAL always not progressive ?

Initial Biopsy → (6 - 7 yrs) → **Final Biopsy**

European Journal of Gastroenterology & Hepatology 2005, 17:1263–1264

Occurrence of hepatocellular carcinoma in an apparently 'healthy' HCV patient

Claudio Puoti, Lia Bellis, Francesca Martellino, Laura Durola, Lucia Spilabotti, Orlando Dell'Unto, Alessandra Galossi and Riccardo Guarisco, Department of Hepatology and Internal Medicine, Marino Hospital, Rome, Italy.

F0	85%
F1	15%

F0	11 %
F1	81 %
F2	8 %

F2 →

F1	20 %	
F2	50 %	
F3	20 %	30%
F4	10 %	

Cividini et al, 2001
Hui et al, 2003
Boccato et al, 2004
Ryder et al, 2004
Okanoue et al, 2005
Puoti et al, 2005

Impact of Steatosis on Progression of Fibrosis in Patients With Mild Hepatitis C

Fartoux Hepatology 2005

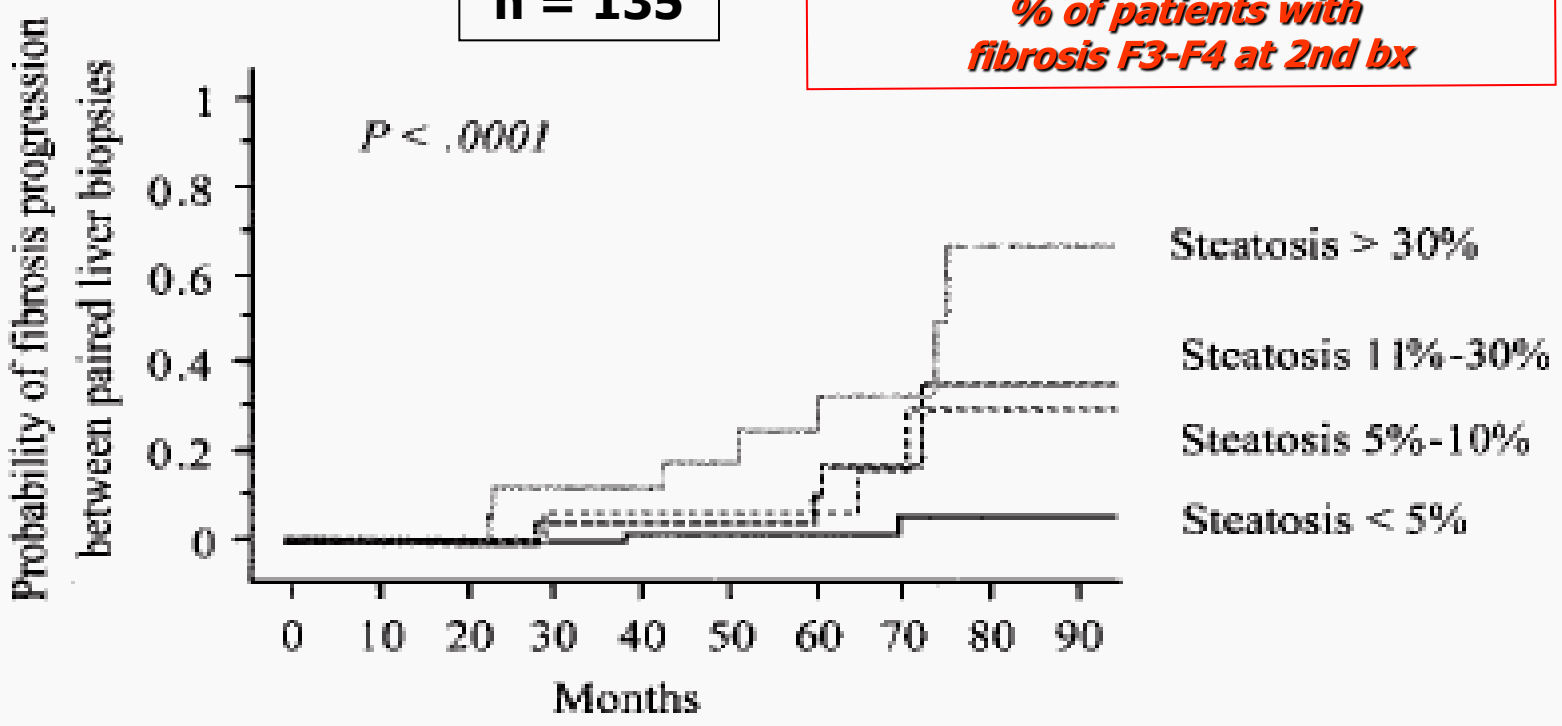
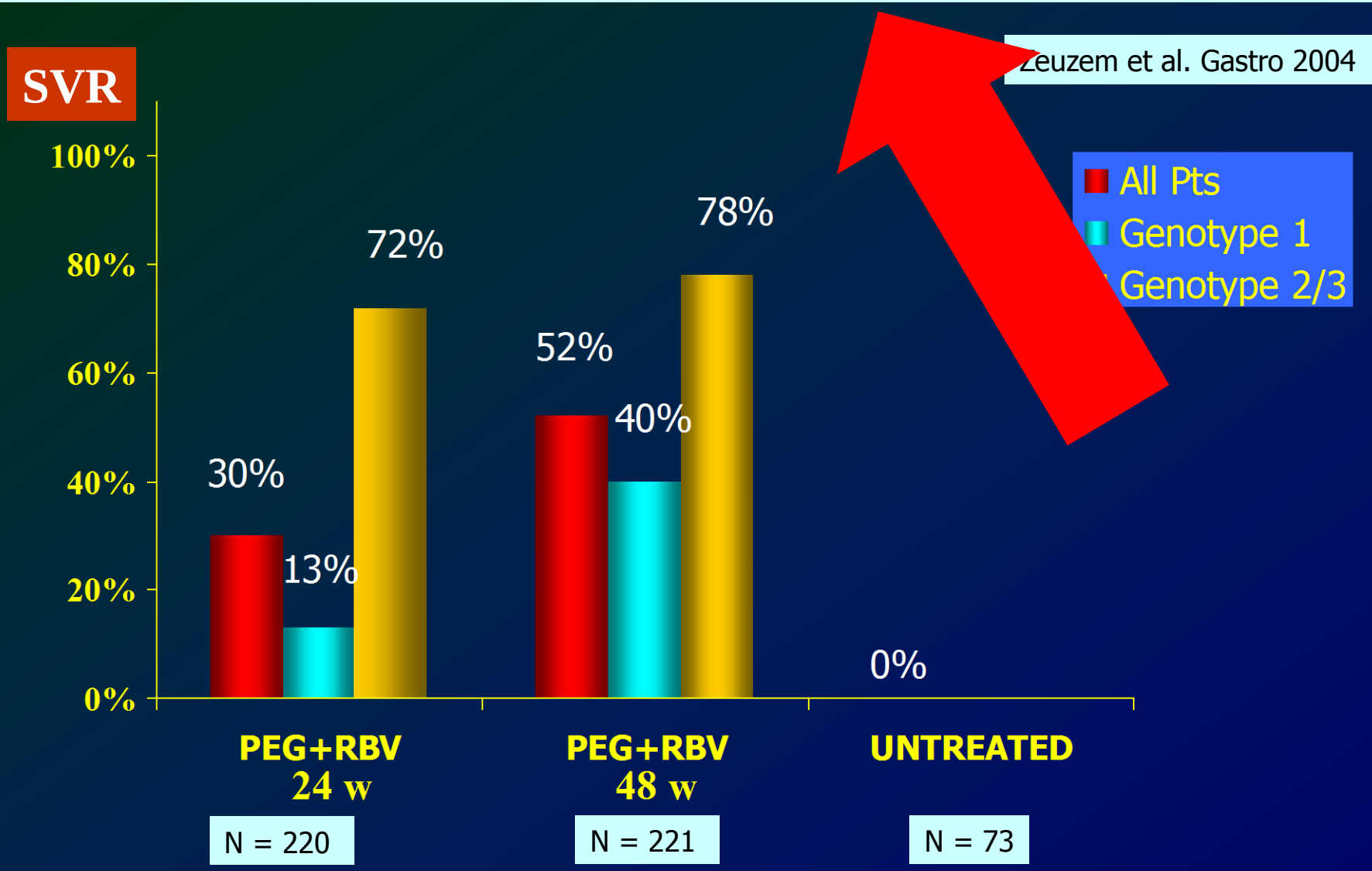


Fig. 2. Cumulative probability of progression of fibrosis according to the percentage of steatosis at initial liver biopsy.

Peginterferon alfa-2a (180 µg qw) plus ribavirin (800 mg qd)



Zeuzem et al. Gastro 2004

Liver International ISSN 1478-3223

CLINICAL STUDIES

Predicting efficacy and safety outcomes in patients with hepatitis C virus genotype 1 and persistently 'normal' alanine aminotransferase levels treated with peginterferon α-2a (40KD) plus ribavirin

Eric Snoeck[1], Stephanos J. Hadziyannis[2], Claudio Puoti[3], Mark G. Swain[4], Thomas Berg[5], Patrick Marcellin[6], Jean-Pierre Zarski[7], Karin Jorga[8] and Stefan Zeuzem[9]

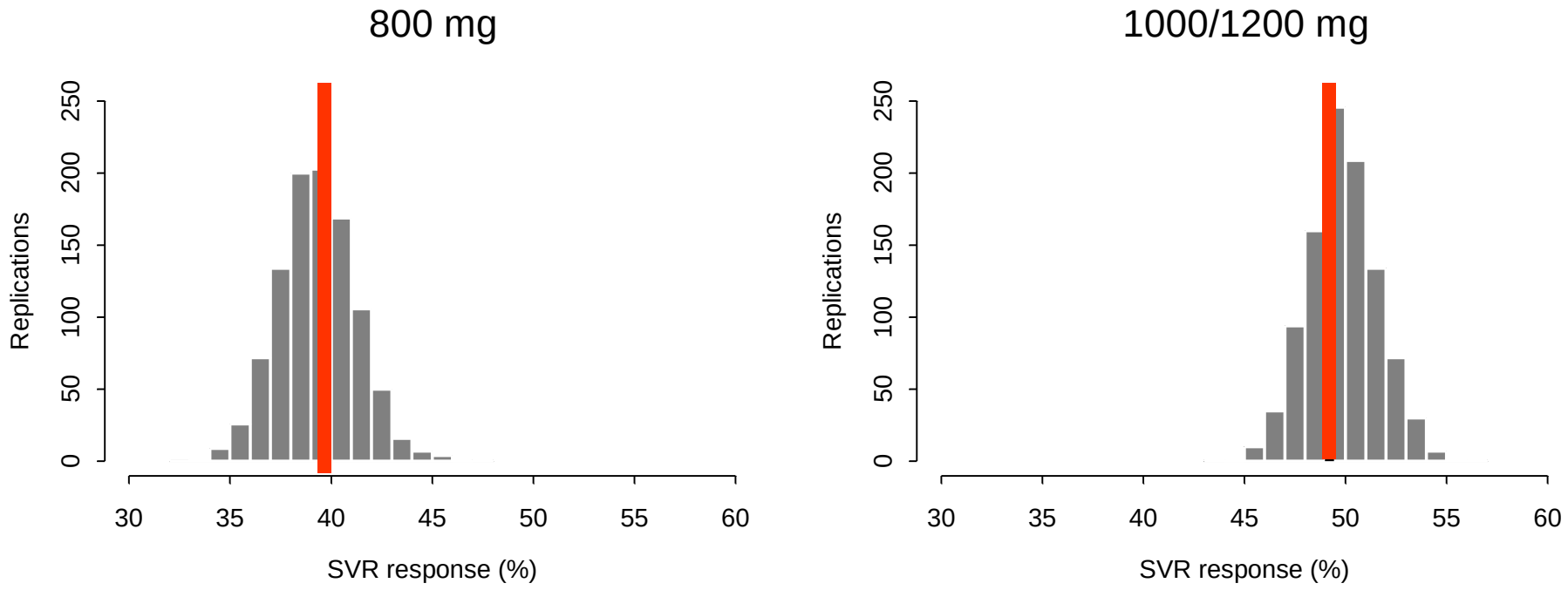
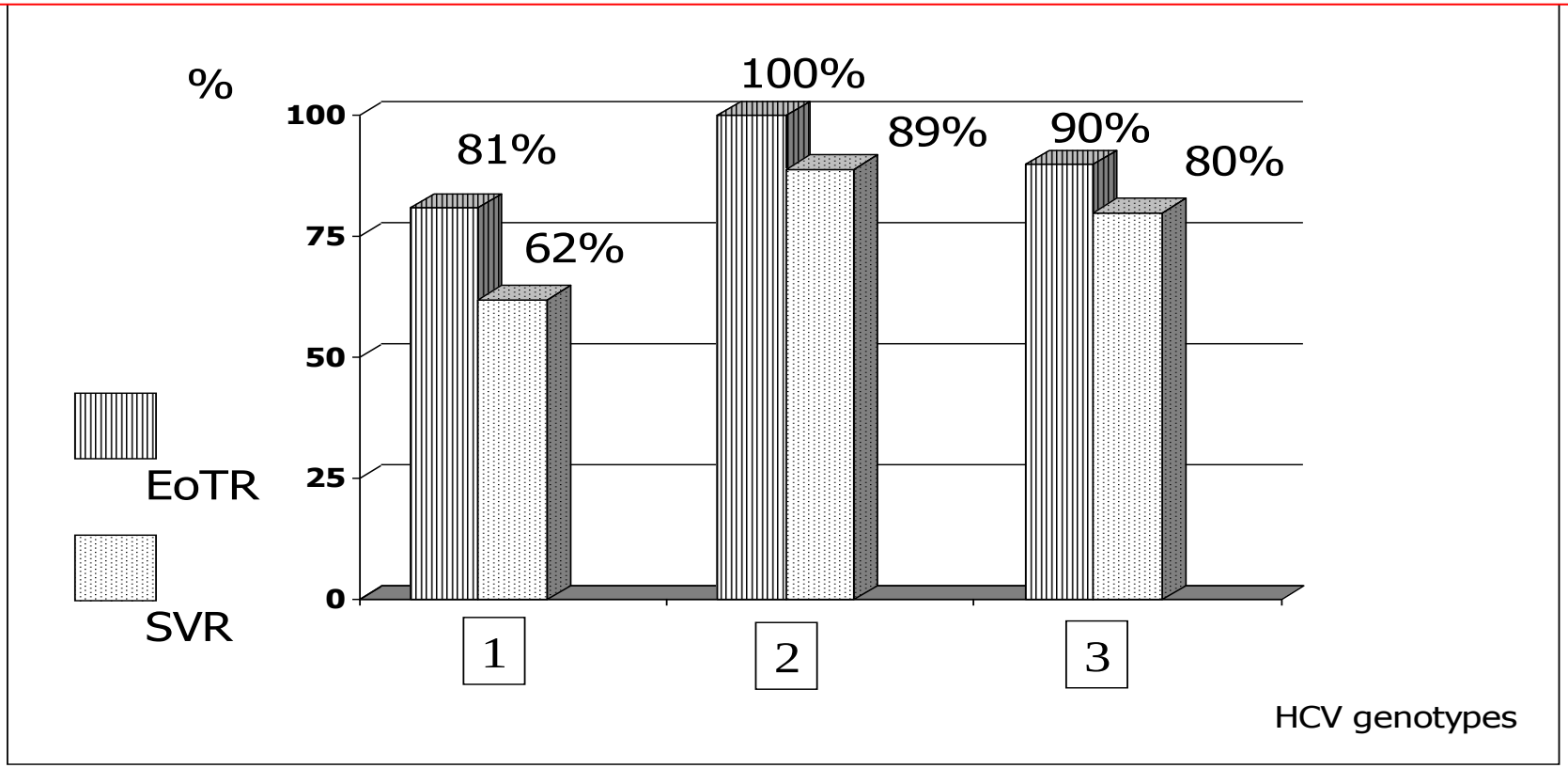


Fig. 1 - Predicting SVR by GAM (generalised additive models) in HCV-1 patients with PNALT treated with 1200 mg of RBV

Liver Int, 2009

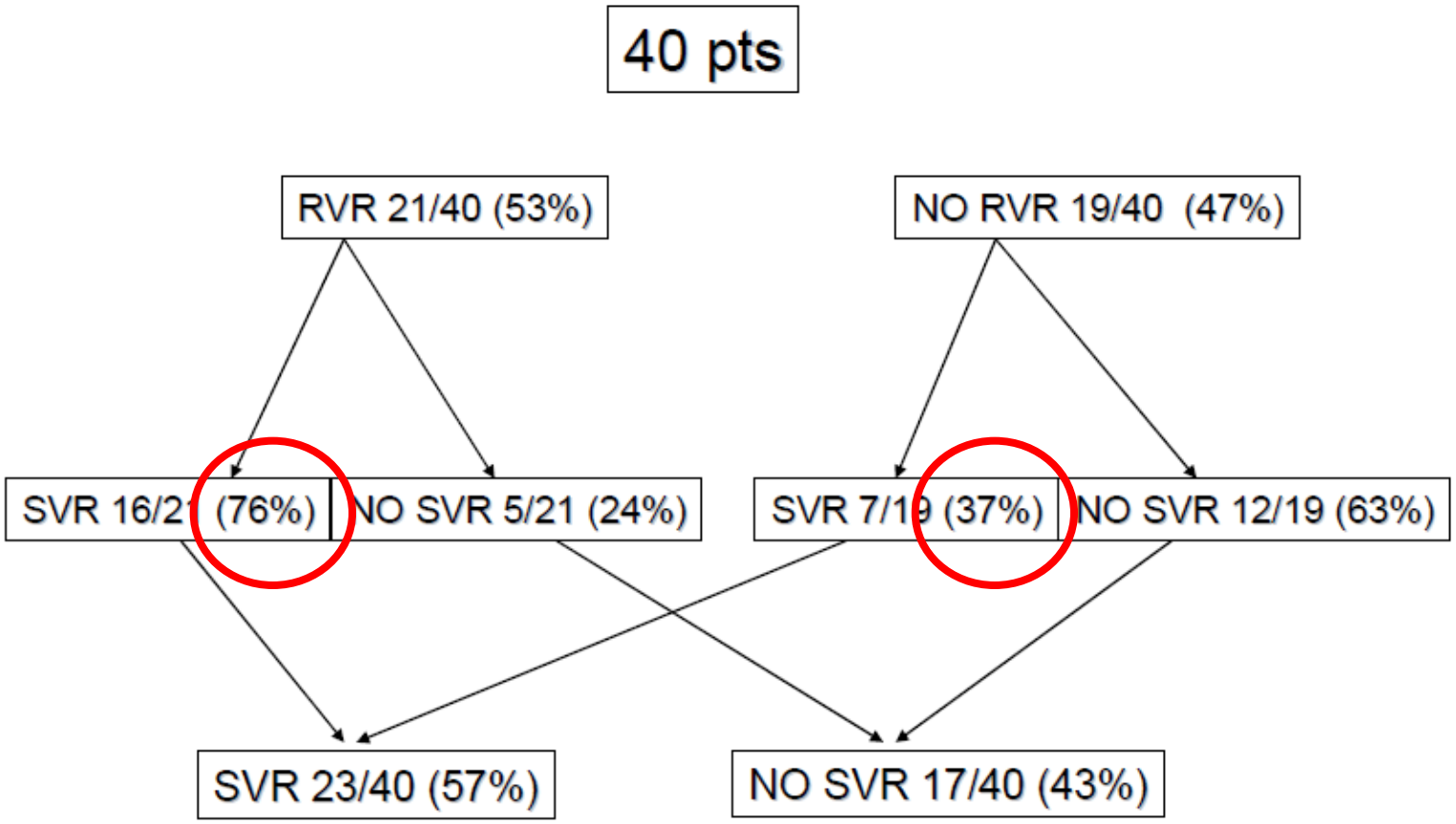
Treatment of hepatitis C virus carriers with persistently normal alanine aminotransferase levels with peginterferon α-2a and ribavirin: a multicentric study

Claudio Puoti[1], Adriano M. Pellicelli[2], Mario Romano[3], Fabrizio Mecenate[4], Riccardo Guarisco[1], Giorgio Barbarini[5], Ettore Mazzoni[6], Lucia Spilabotti[1], Lia Bellis[1], Federica Paglia[1], Angelo Barlattani[7], Antonio Picardi[8], Amerigo Paffetti[9], Maria Elena Bonaventura[10], Lorenzo Nosotti[11], Olga Mitidieri[12], Orlando Dell' Unto[1], Roberto Villani[2], Chiara Dell' Unto[1], Aldo Morrone[13] and Fabrizio Soccorsi[2], on behalf of the Club Epatologico Ospedaliero (Hospital Liver Club – CLEO)



JOURNAL OF VIRAL HEPATITIS
JVH
Journal of Viral Hepatitis, 2010

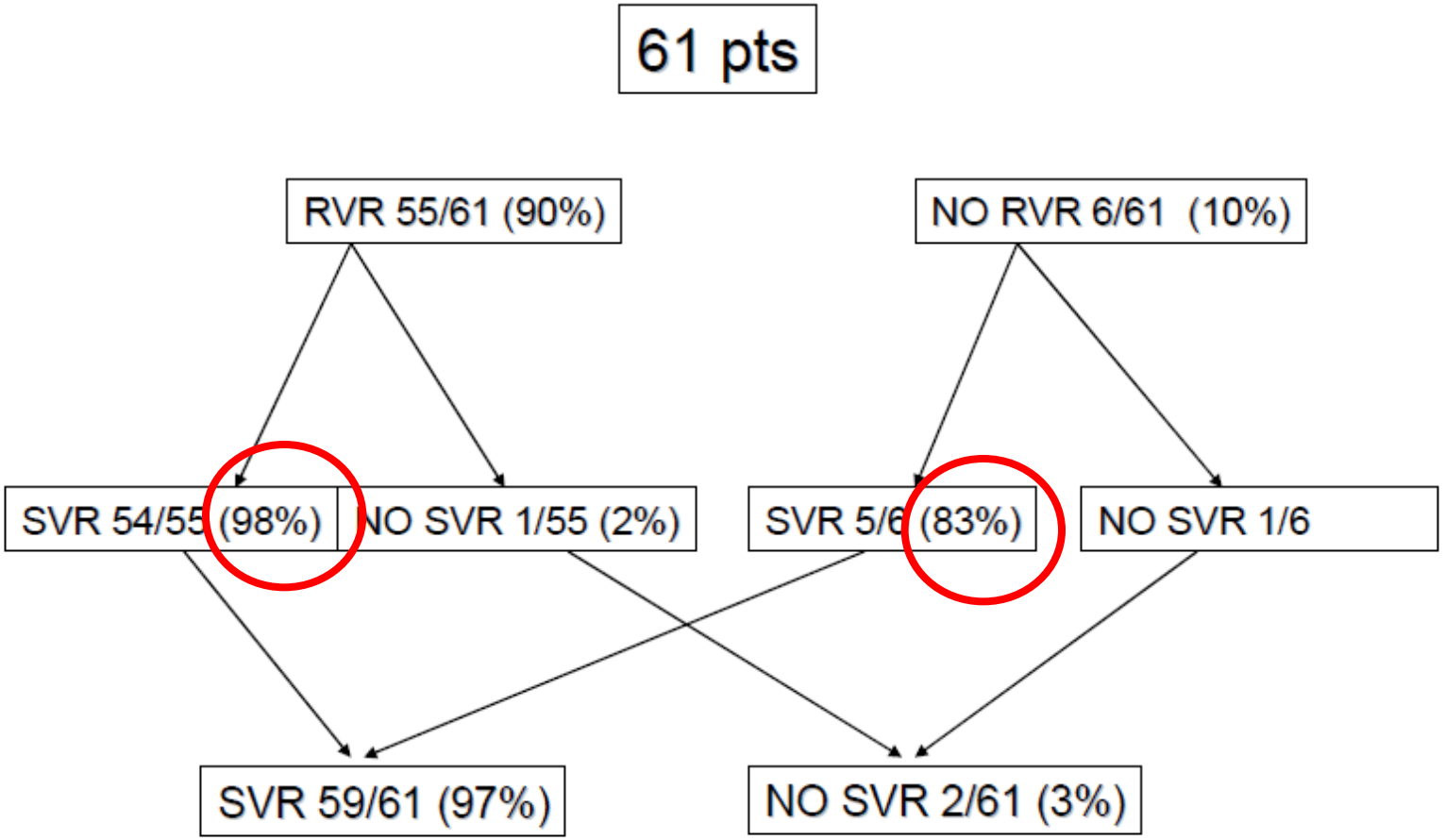
Rates of SVR according to the presence or absence of RVR in HCV-1



Puoti et al JVH 2010

JOURNAL OF VIRAL HEPATITIS
JVH
Journal of Viral Hepatitis, 2010

Rates of SVR according to the presence or absence of RVR in HCV-2



Puoti et al JVH 2010

Predictors of SVR (univariate analysis)

Gender (female)
Baseline viral load <800.000 IU
Non-1 genotype
BMI < 24
RVR yes

Puoti C et al, Liver Int 2009

Predictors of SVR (multivariate analysis)

Gender (female)
Baseline viral load <800.000 IU
Non-1 genotype
BMI < 24
RVR yes

Puoti C et al, Liver Int 2009

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive and Liver Disease 42 (2010) 745–747

Correspondence

Sustained virological response following extremely short antiviral treatment in selected HCV carriers with persistently normal ALT

C. Puoti*
R. Guarisco
L. Spilabotti
L. Bellis
Dept of Internal Medicine and Liver Unit, Marino

We report here our experience in a very small group of HCV patients achieving sustained virological response (SVR) after an unusually short course of antiviral treatment with peginterferon (PEG-IFN) alpha-2a and ribavirin (RBV), due to early and unexpected discontinuation of therapy.

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

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Digestive and Liver Disease 42 (2010) 745–747

Six females HCV pos
Mean age 28±3 years, range 18–39 years
Mean ALT 18±10 IU/L, range 12–36 IU/L
Genotype HCV-2
Mean HCV RNA 210×10^3 IU/mL

Bx 3/6 (2 normal liver, 1 F1)
Stiffness 4.7±2.0 kPa, range 3.0–6.1 kPa

- All patients began antiviral treatment with PEG IFN alfa 2a once weekly plus RBV 800 mg/day for a scheduled period of 24 weeks.

- At wk 4 all the 6 patients had RVR

- Treatment was unexpectedly discontinued shortly thereafter (mean duration *5.5±1.5 wks, range 4–7*) because of :

- psychiatric manifestations, 1;
- severe pyrexia, 1;
- fatigue and other constitutional symptoms, 2
- personal problems, 2 (loss of employment and divorce)

- All patients began antiviral treatment with PEG IFN alfa

HCV RNA was further determined at 12, 24 and 48 weeks from the last administration of antiviral medication, remaining negative throughout follow-up in all patients.

To date no relapse has occurred, confirming HCV eradication

- personal problems, 2 (loss of employment and divorce)

Elevation of ALT is not a requirement for therapy of CHC

NIH *Consensus Conference 2002,* ***AASLD*** *Guide-Lines 2004,* ***AGA*** *Technical Review 2006,* ***AISF*** *2006*

Decision making should rely on *individual patient features:*

- genotype and histology
- age of the patient
- potential progression of disease
- probability of viral eradication
- co-morbid illness and co-factors
- risk of HCV transmission
- patient motivation, desire for pregnancy
- QoL and social/psychological stigma
- major concerns over infectivity

ALT levels may have less importance in deciding who should be treated

The Cost/Benefit issue

Priority needs to be defined

- It is really impossible to perform liver biopsy in all HCV patients with PNALT.
- The cost of treating all is exceedingly high.
- Cost/benefit might be particularly favourable in :
  - *young, easy to treat patients (high rate of SVR with short therapy)*
  - *middle age patients with "significant" liver disease (at risk of developing end stage liver disease)*

Puoti C, J Gastrointest Liver Dis 2007

The age issue

Younger patients:

- respond to / tolerate therapy better
- have longer life expectancy
- are often well motivated
- usually have minimal disease
- have fewer contraindications

Decision based more on expected response and motivation than on liver disease

Puoti C, Hepatology 2009

The age issue

Older patients:

- respond less well to therapy
- more frequently have significant liver disease and / or co-factors
- often have longer infection / disease duration
- may experience more side effects
- might be less motivated

Decision more based on disease

Puoti C, Hepatology 2009

Progress Report

Practice guidelines for the treatment of hepatitis C: Recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting☆

Digestive and Liver Disease 42 (2010) 81–91

- Decision making should rely on individual characteristics such as genotype, histology, age, potential disease progression, the probability of viral eradication, patient motivation, the desire for pregnancy, comorbidities, co-factors, etc. (A-VI).
- Antiviral treatment might be offered without the need for liver biopsy in patients with a high likelihood of achieving an SVR (e.g. an age of <50 years + easy-to-treat HCV genotype + low viral load), in the absence of any contraindication and co-factors of poor responsiveness (A-VI).
- In patients aged 50–65 years, and in those with a reduced likelihood of achieving an SVR, a liver biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis (>F2) and a higher possibility of response, depending on the HCV genotype (A-VI).

Progress Report

Practice guidelines for the treatment of hepatitis C: Recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting☆

Digestive and Liver Disease 42 (2010) 81–91

Biopsy and therapy are not recommended in therapy elderly (>70 years). These patients should be recommended to adopt lifestyle changes and undergo periodic ALT determinations (D-VI).

Non-invasive assessments of fibrosis can be used to detect changes over time and consequently indicate the need for biopsy or treatment on an individual patient basis.

In patients not receiving antiviral treatment, periodic ALT measurements and adequate lifestyles should be recommended. In particular, overweight and the use of alcohol should be strongly discouraged.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Management of Incidental Hepatitis C Virus Infection

A 25-year-old black woman is referred to your clinic for management of an incidental positive result on a hepatitis C virus (HCV) antibody test. She had decided to donate blood because her mother had recently become ill and required a transfusion. Three weeks after her donation, she received a telephone call and was told that her donated blood could not be used because her HCV antibody test was positive. She was encouraged to see her primary care physician to determine whether anything further should be done.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Management of Incidental Hepatitis C Virus Infection

ALT 31 U/l (normal range, 7 to 52)
AST 30 U/l (normal range, 9 to 30)
WBC 2600/mmc
PLT 175.000/mmc
Hb 11.0 g/dL
HBsAb positive

HCV-1
HCV RNA 2.3 x 10^6/mL

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Management of Incidental Hepatitis C Virus Infection

When the patient returns to discuss follow-up, you administer the hepatitis A vaccine and counsel her to minimize exposure to potential hepatotoxic factors such as alcohol and excessive use of acetaminophen.

In addition, which one of the following treatment options for HCV infection, any of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

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CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Management of Incidental Hepatitis C Virus Infection

1. Expectant management with periodic assessment of liver function.
2. Liver biopsy, with treatment based on the findings.
3. HCV therapy with peginterferon and ribavirin.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

INTERACTIVE AT NEJM.ORG

Management of Incidental Hepatitis C Virus Infection

TREATMENT OPTION 3

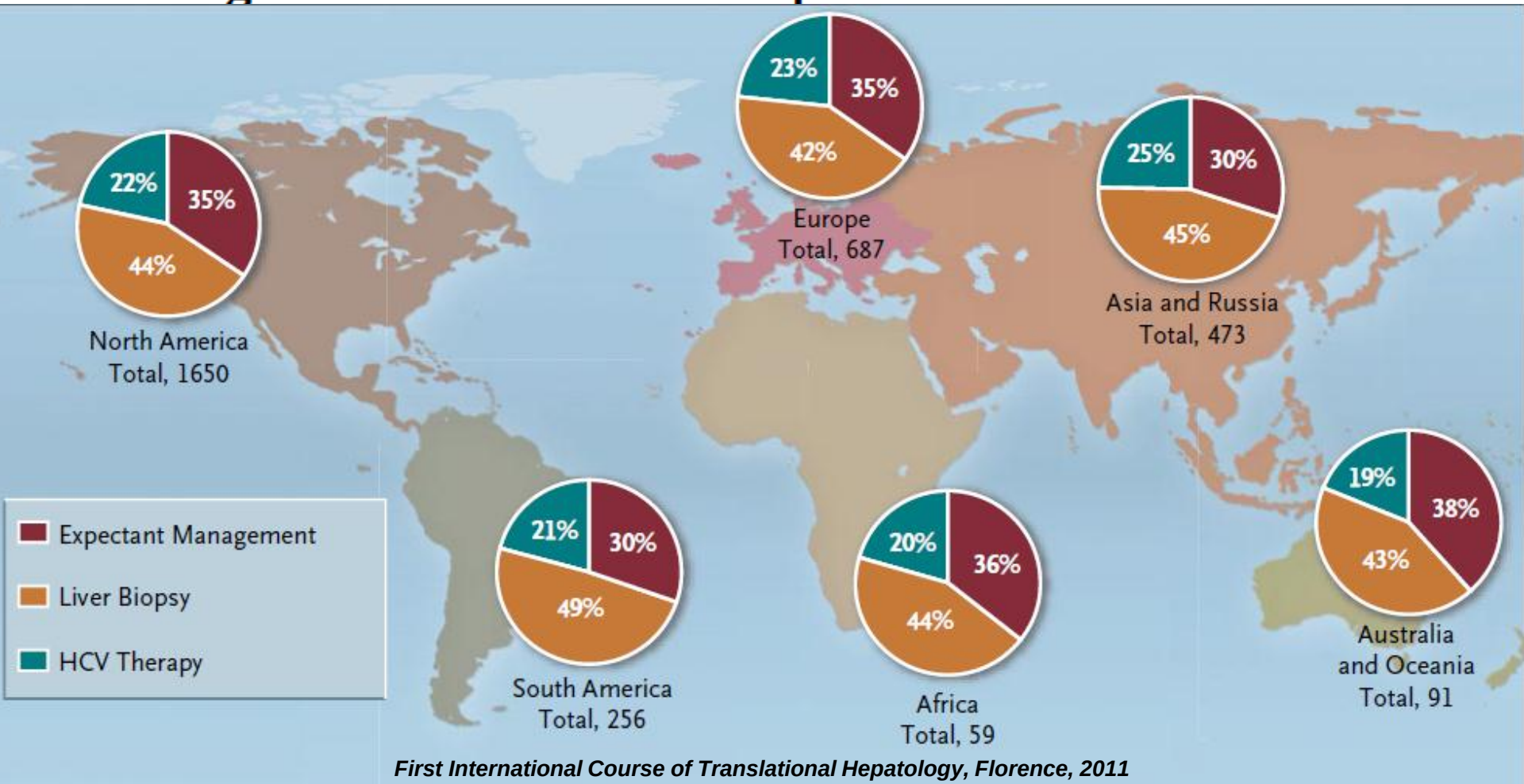
HCV Therapy with Peginterferon and Ribavirin

Adrian M. Di Bisceglie, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL DECISIONS

Management of Incidental Hepatitis C Virus Infection —



The future

… and miles to go before we sleep

1. Better tailoring to optimize therapy
2. Identifying candidates to liver biopsy
3. Role of non-invasive methods for the assessment of hepatic fibrosis
4. Shorter treatments on the basis of rapid (4^{th} wk) and early (12 wk) virological responses
5. Predictive value of IL28B polymorphism in PNALT
6. Impact of new therapies ?

Thank you for your kind attention !