Gianni Testino

Centro Alcologico Regionale – Regione Liguria

UO Alcologia e Patologie Correlate

Dipartimento Medicina Interna e Specialistica

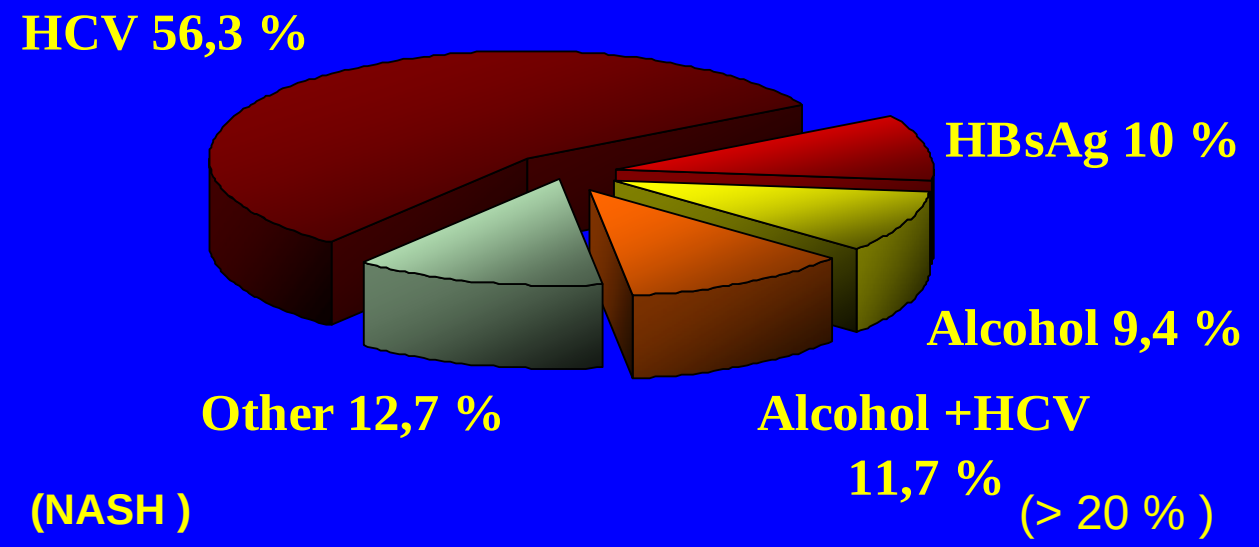
Area ad Integrazione con il Territorio

IRCCS Ospedale San Martino-Istituto Tumori, Genova

Societa' Italiana di Alcologia

Alcol, etica e trapianto

CHRONIC LIVER DISEASE



Sagnelli E. et al. J Med Virol 2005

Epatopatia Alcol Correlata

44% di tutti i decessi per cirrosi e' alcol correlata

O'Shea et al,Hepatology 2010; 51:308-328

Associazione Alcol/HCV nel 30% dei casi (Testino G et al, 2008)

RAPPORTO 2012 ISS – Osservatorio Nazionale Alcol-CNESPS
RELAZIONE MINISTRO DELLA SALUTE AL PARLAMENTO – Dicembre 2011

129.1 ricoveri ogni 100000 ab. (50% epatopatia, 36.4% cirrosi)

Mortalita' per cirrosi epatica importante indicatore di danno alcol correlato

Attribuibili all'uso dannoso di alcol il 59.3% dei decessi per cirrosi tra i maschi e il 48.7% tra le donne
Valore massimo fra i 45-64 anni di entrambi i sessi

APPROPRIATEZZA DELLA DIAGNOSI DI DIPENDENZA ALCOLICA

Epatopatia alcol-correlata

75% diagnosi di dipendenza alcolica

Lucey, Merion, Beresford 1994

P. Burra, 2007

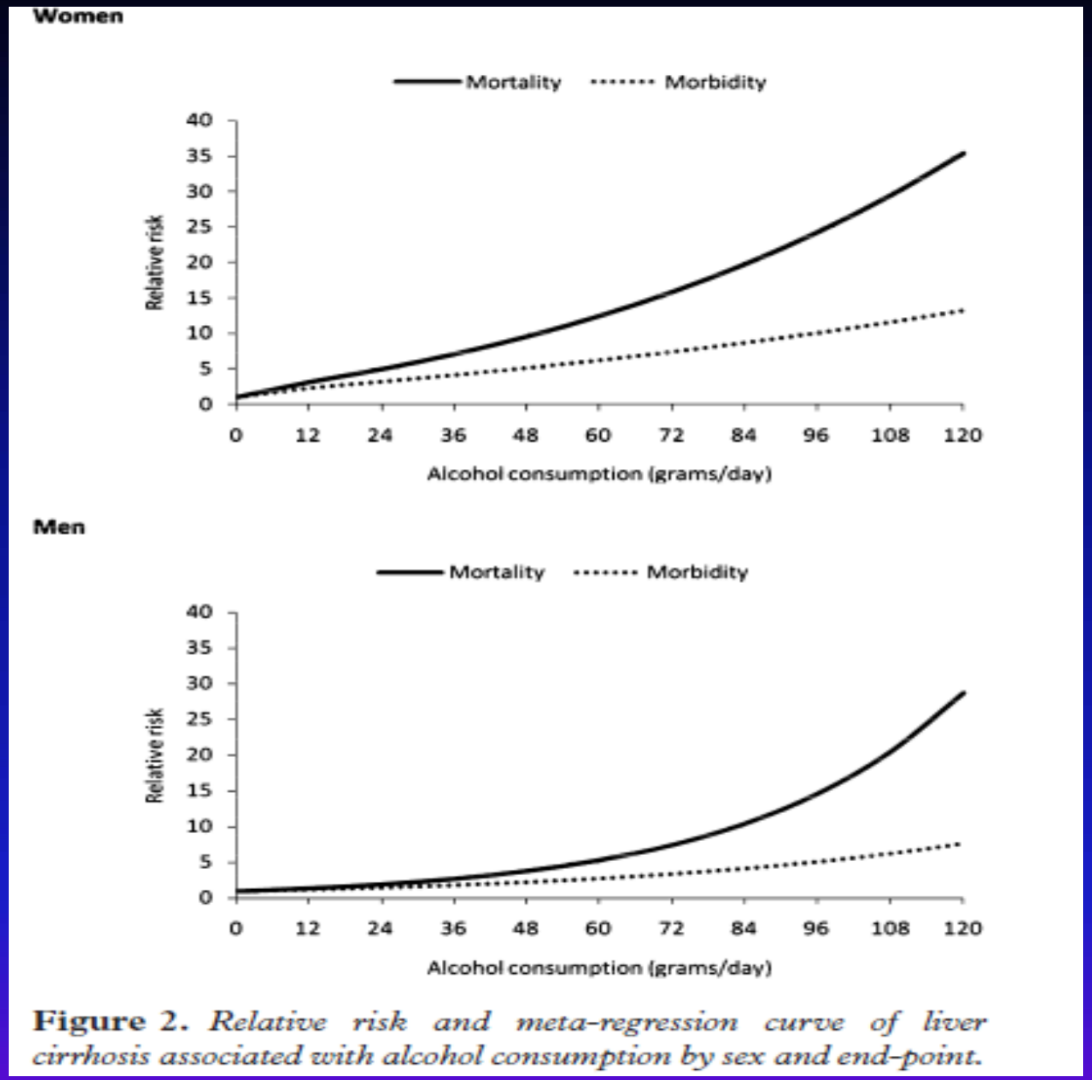


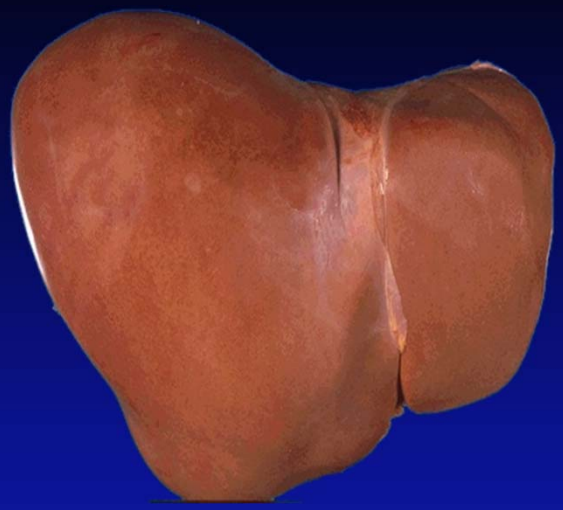
Figure 2. *Relative risk and meta-regression curve of liver cirrhosis associated with alcohol consumption by sex and end-point.*

Rehm et al, Drug and Alcohol Review 2010

Alcohol intake g/day	RR	(95% CI)
0	1,0	Reference
25	1,9	1,6-2,3
50	3,6	2,5-5,1
100	13,1	6,5-26,5
150	47,2	16,4-136,1
200	170,7	41,6-700,0

Corrao et al, Alcohol and Alcoholism 1998

gr/die ⟶



12-20 women, 25-80 men

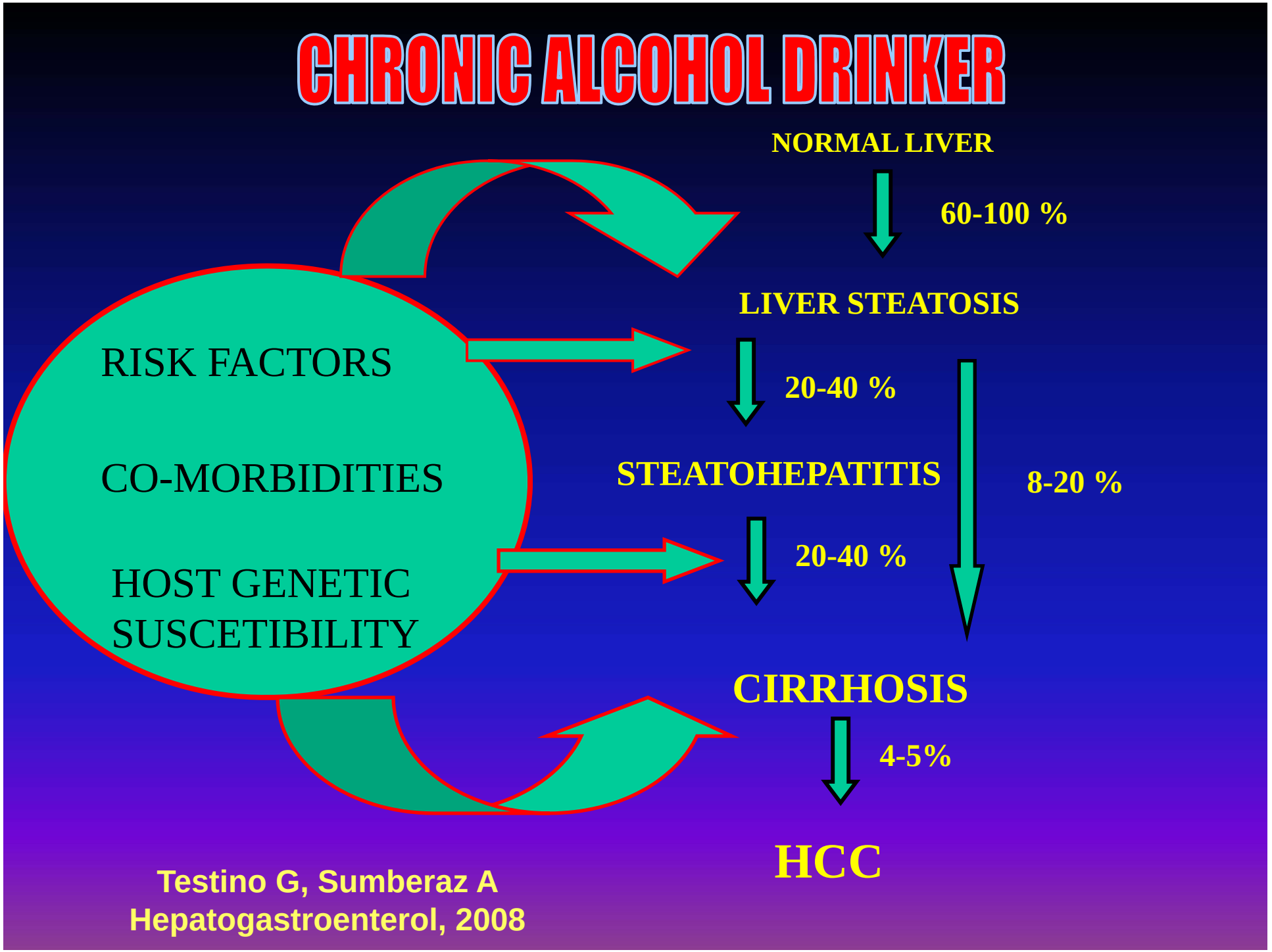
O'Shea, 2010

Daily Alcohol Intake > 30 g/day

Odds of developing cirrhosis or lesser degrees of liver disease

cirrhosis: 13.7; lesser degrees: 23.6

Bellentani et al, 1997


CHRONIC ALCOHOL DRINKER
NORMAL LIVER
60-100 %
LIVER STEATOSIS
20-40 %
STEATOHEPATITIS
20-40 %
8-20 %
CIRRHOSIS
4-5%
HCC
RISK FACTORS
CO-MORBIDITIES
HOST GENETIC SUSCETIBILITY
Testino G, Sumberaz A
Hepatogastroenterol, 2008

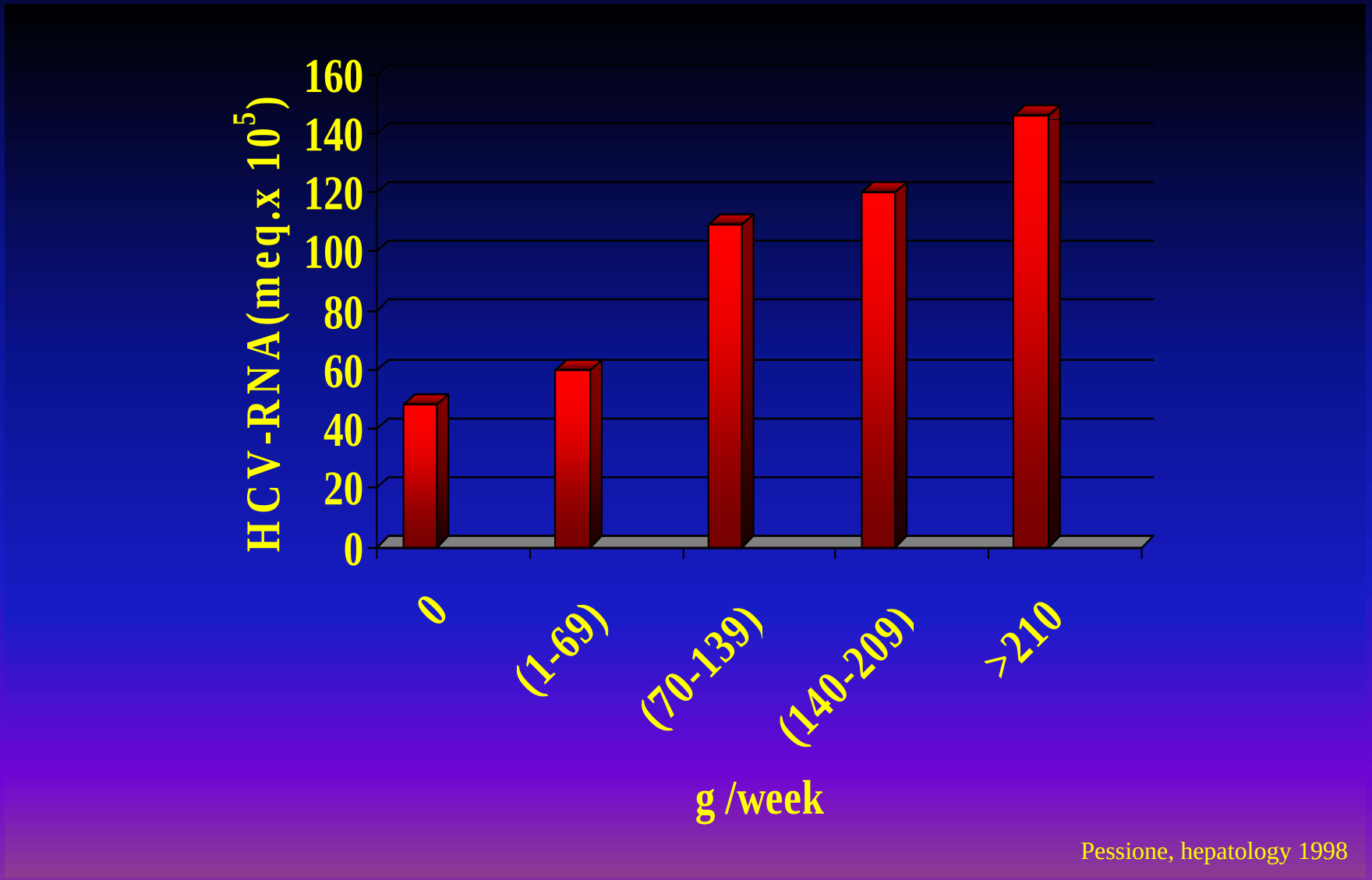
PREDISPOSITION TO ALCOHOLIC LIVER DISEASE

Mutations and Polymorphism of genes

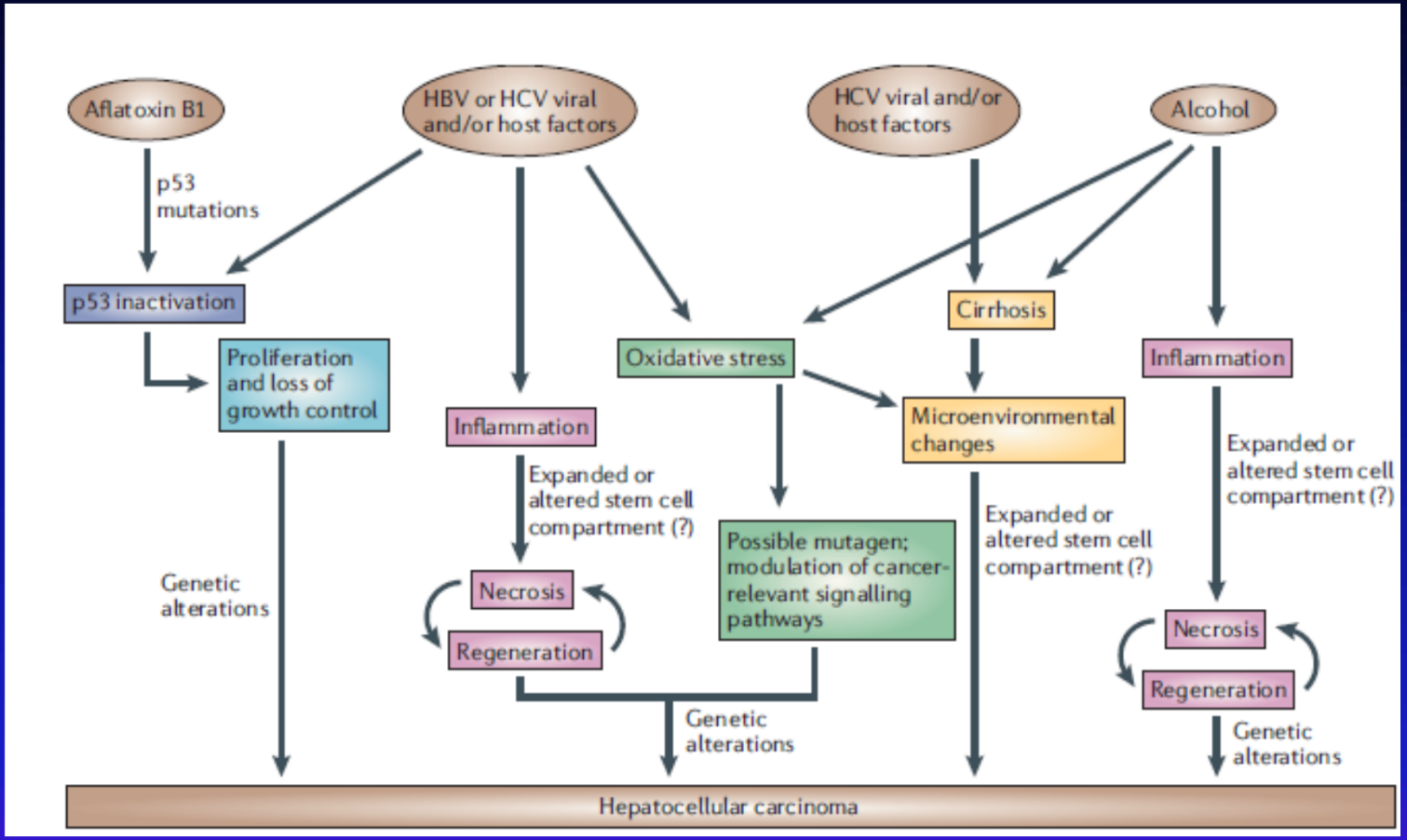
- Ethanol metabolism (ADHs, ALDHs, CYP2E1, Mitochondrial Superoxide Dismutase, Myeloperoxidase)
- Cytokines of the inflammatory response (TNF alpha, TNF alpha promoter polymorphisms, IL1, IL10,TNF-alpha-type-1 receptor,….)
- Polymorphisms in DNA repair genes (DNA ligase III, DNA polymerase b, poly-ADB-ribose-polymerase….)
- Genes involved in estrogen synthesis and metabolism (CYP17, CYP19, CYP1B1, catechol-0-methyltransferase)
- Polymorphisms in methylenetetrahydrofolate reductase
- GABA-ergic, dopaminergic, serotoninergic systems
- Components of immune systems (innate, adaptive)

IARC, 2010

EFFETTI DELL'ALCOOL SU HCV-RNA



Pessione, hepatology 1998



Farazi et al, Nature 2006

Variables	Progressive fibrosis ($n = 44$)	Non-progressive fibrosis ($n = 34$)	
Sex (M/F)	28/16	16/18	
Transmission route (IDU/BT/SEX/HCW/unknown)	16/12/3/2/1	16/10/1/2/5	
Genotype (1/2/3/unknown)	19/11/12/2	18/4/10/2	
Age at initial biopsy (years)	36.8 (27.1–44.3)	34.0 (28.1–43.5)	
Age at follow-up biopsy (years)	43.7 (38.5–50.6)	39.0 (35.4–46.0)	
Time between first and follow-up biopsy (years)	6.5(3.9–10.6)	5.5 (2.5–7.7)	
Total amount of alcohol (g ethanol)	15 400 (3300–36 600)	3900 (900–14 500)	$P = 0.007$*
Alcohol per day (g ethanol)	5.7 (2.0–16.0)	2.6 (1.1–7.7)	$P = 0.03$*
Drinking frequency (drinking days/year)	34.5 (21.0–75.0)	8.2 (6.0–25.0)	$P = 0.006$*
Quantity consumed on each occasion (drinks/occasion)	4.0 (3.0–8.0)	3.0 (2.0–6.0)	

Westin et al, J Viral Hep 2002

Table 1: Patient survival after liver transplantation.

Diagnosis	1-year survival (%)	No. of patients	3-year survival (%)	No. of patients	5-year survival (%)	No. of patients	10-year survival (%)	No. of patients
Hepatitis C								
Burra et al. [25]	81	4166			67	1906	54	475
Aguilera et al. [24]	72	68			49	83		
Dhar et al. [20]	80	25						
Alcoholic Liver Disease								
Burra et al. [25]	84	6301			73	2867	58	663
Aguilera et al. [24]	90	96			76	81		
Burra et al. [21]			64	33				
Dhar et al. [20]	90	22						
Pera et al. [22]	83	29						
Goldar-Najafi et al. [23]	93	52						
Hepatitis C + Alcoholic Liver Disease								
Burra et al. [25]	84	714			65	261	52	57
Aguilera et al. [24]	86	51			73	43		
Burra et al. [21]			82	16				
Dhar et al. [20]	72	7						
Pera et al. [22]	88	21						
Goldar-Najafi et al. [23]	97	31						

Carbone and Neuberger, Journal of Transplantation 2010

THE SEARCH FOR GENETIC RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

Genetic variation modulating addiction to alcohol

Genetic variation of alcohol-metabolising enzymes

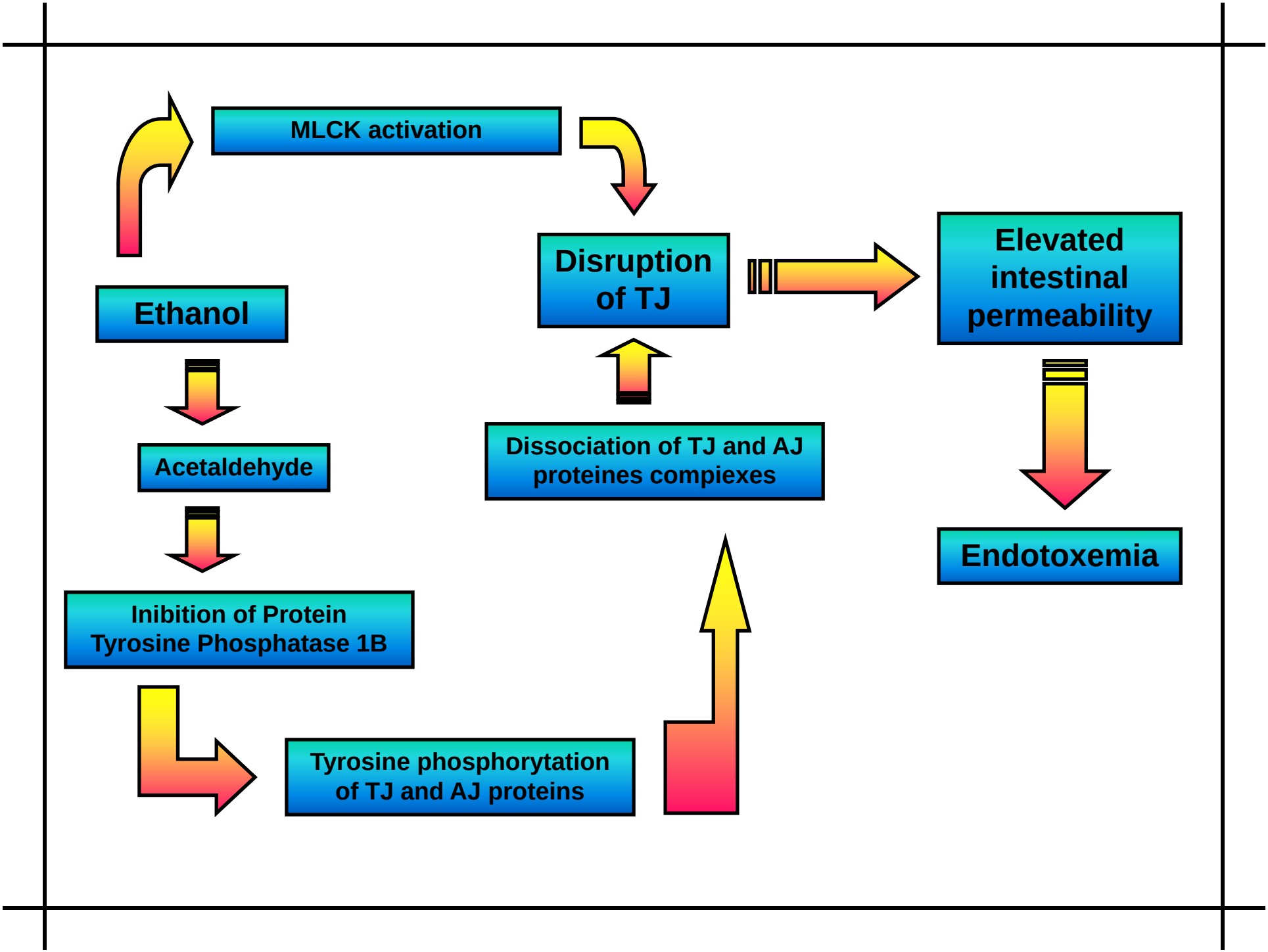
Genetic variations involved in oxidative stress

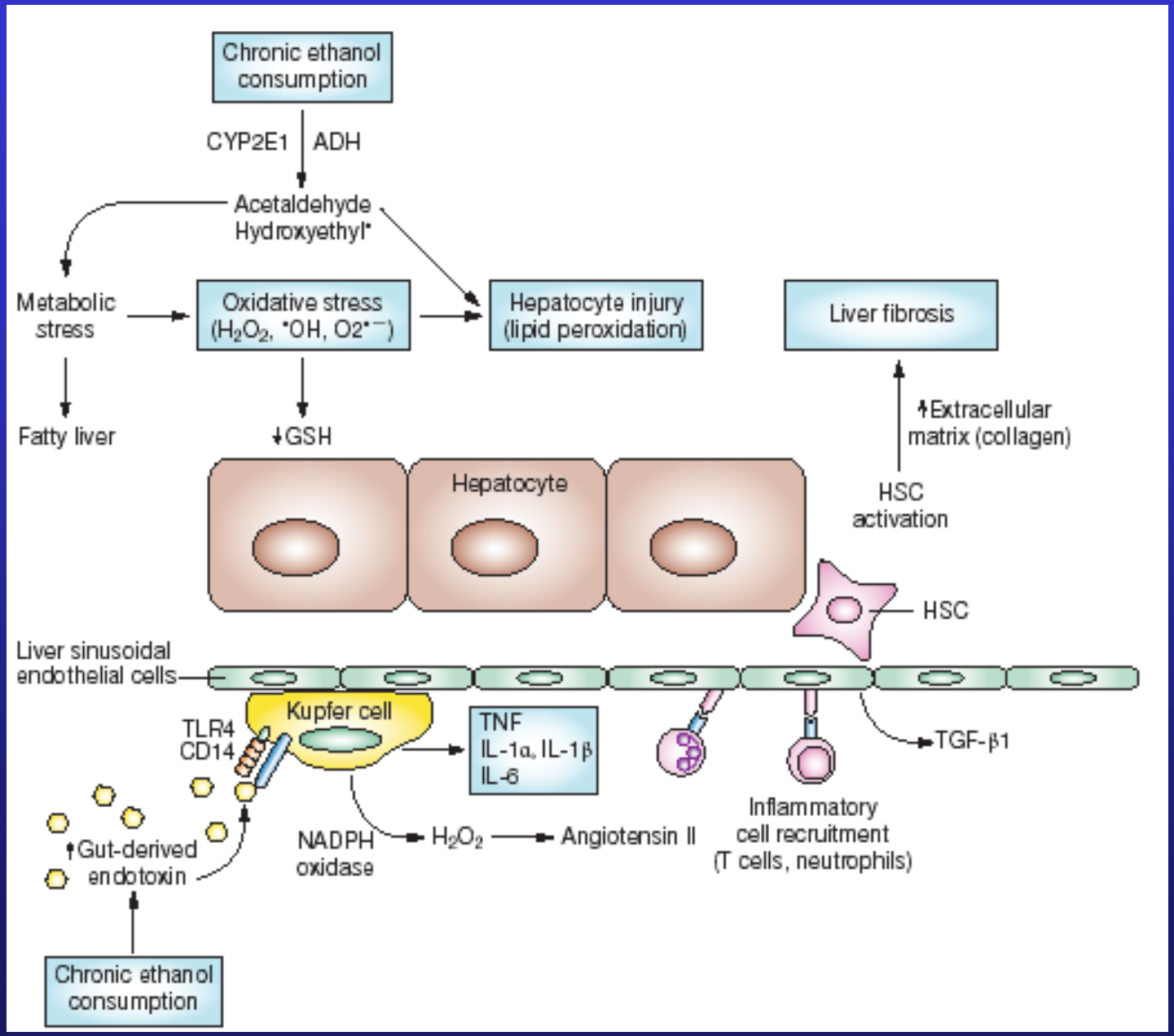
Genetic variations controlling hepatic lipid storage

Genetic polymorphisms modulating endotoxin inflammation

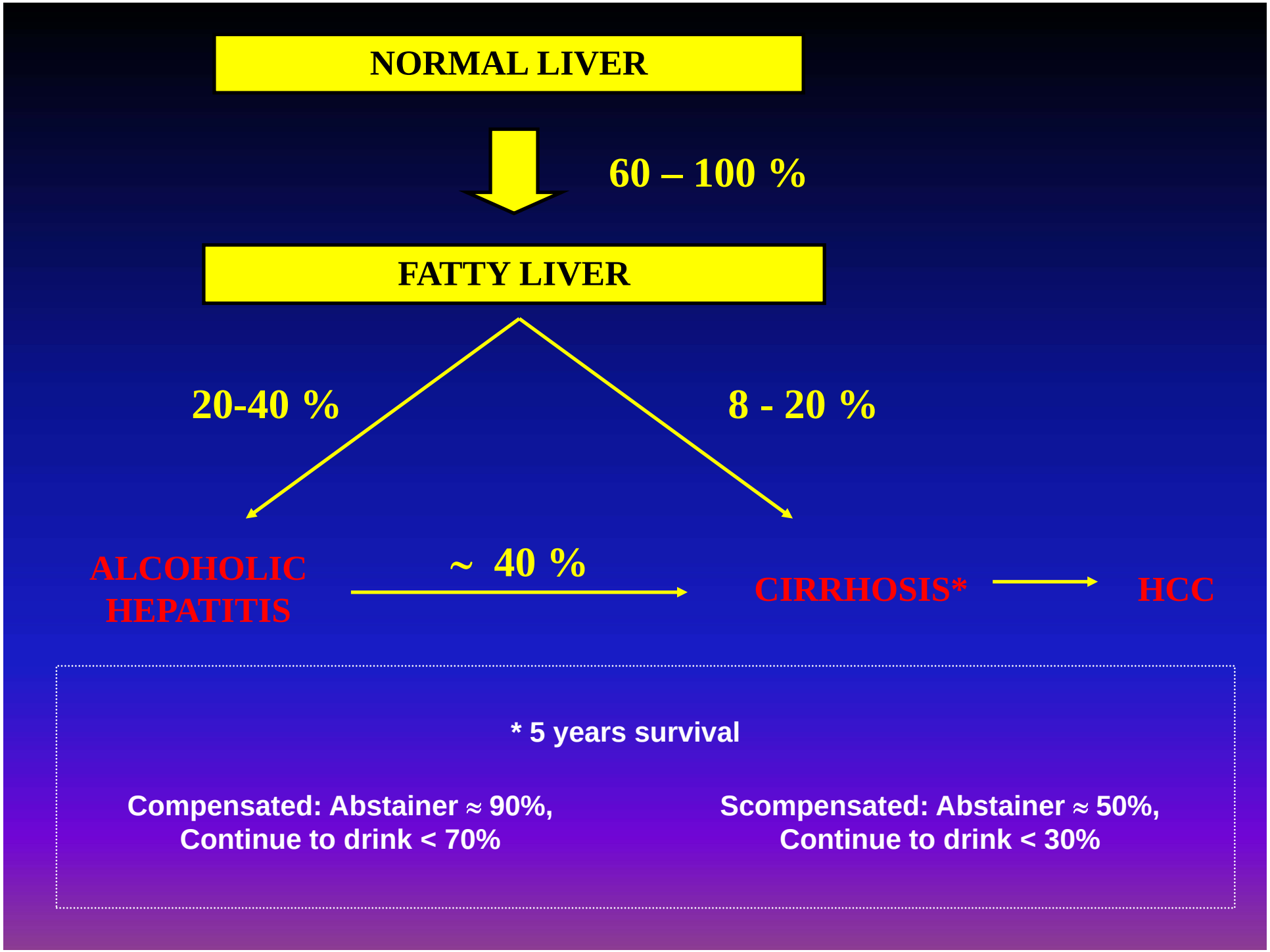
Polymorphic variants of fibrosis-associated genes

Stickel and Hampe, Gut 2011


MLCK activation
Ethanol
Acetaldehyde
Inibition of Protein Tyrosine Phosphatase 1B
Tyrosine phosphorytation of TJ and AJ proteins
Dissociation of TJ and AJ proteines compiexes
Disruption of TJ
Elevated intestinal permeability
Endotoxemia


Chronic ethanol consumption
CYP2E1
ADH
Acetaldehyde
Hydroxyethyl•
Metabolic stress
Oxidative stress (H_2O_2, •OH, $O2^{\bullet -}$)
Hepatocyte injury (lipid peroxidation)
Liver fibrosis
Fatty liver
↓GSH
↑Extracellular matrix (collagen)
Hepatocyte
HSC activation
HSC
Liver sinusoidal endothelial cells
Kupfer cell
TLR4
CD14
TNF
IL-1α, IL-1β
IL-6
TGF-β1
↑Gut-derived endotoxin
NADPH oxidase
H_2O_2
Angiotensin II
Inflammatory cell recruitment (T cells, neutrophils)
Chronic ethanol consumption

Tilg H., 2007


NORMAL LIVER
60 – 100 %
FATTY LIVER
20-40 %
8 - 20 %
ALCOHOLIC HEPATITIS
~ 40 %
CIRRHOSIS*
HCC
* 5 years survival
Compensated: Abstainer ≈ 90%,
Continue to drink < 70%
Scompensated: Abstainer ≈ 50%,
Continue to drink < 30%

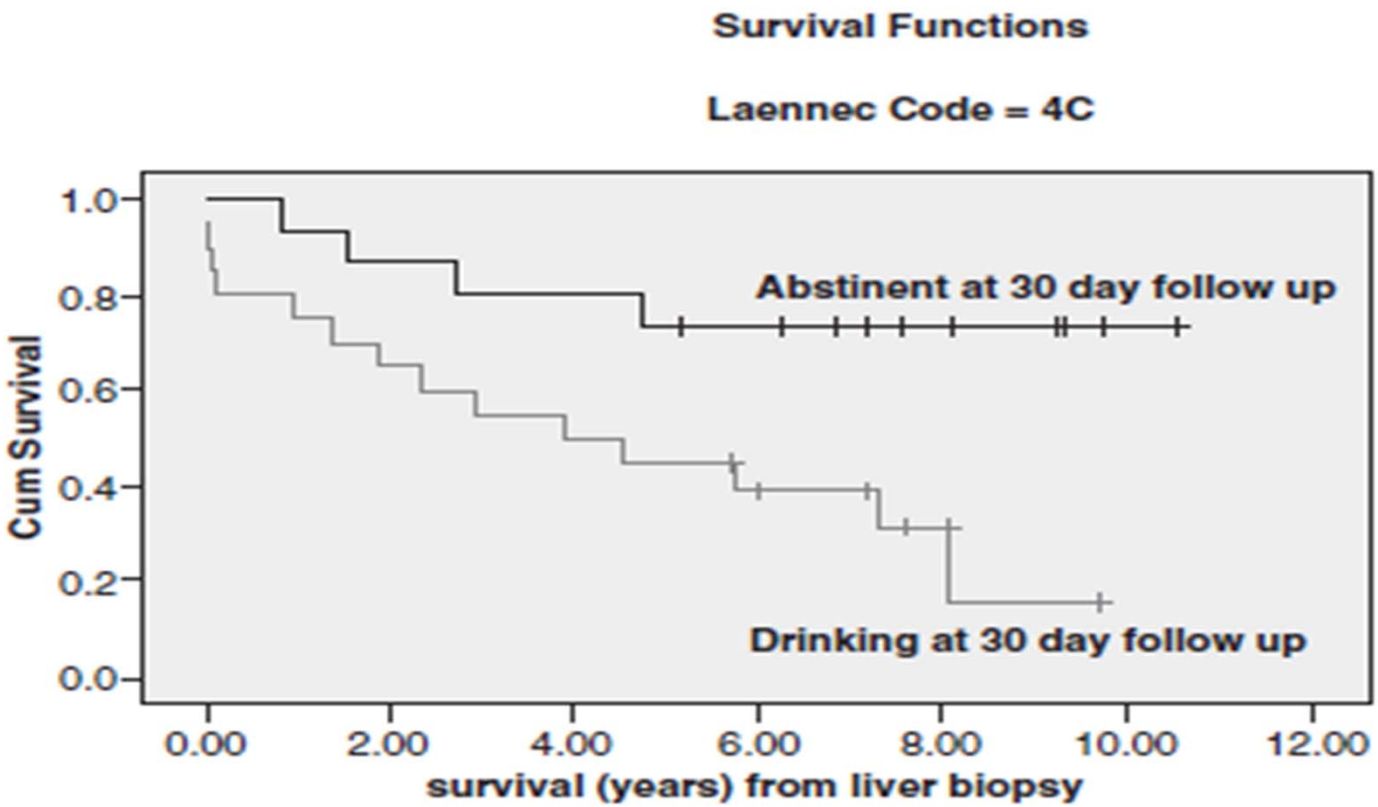
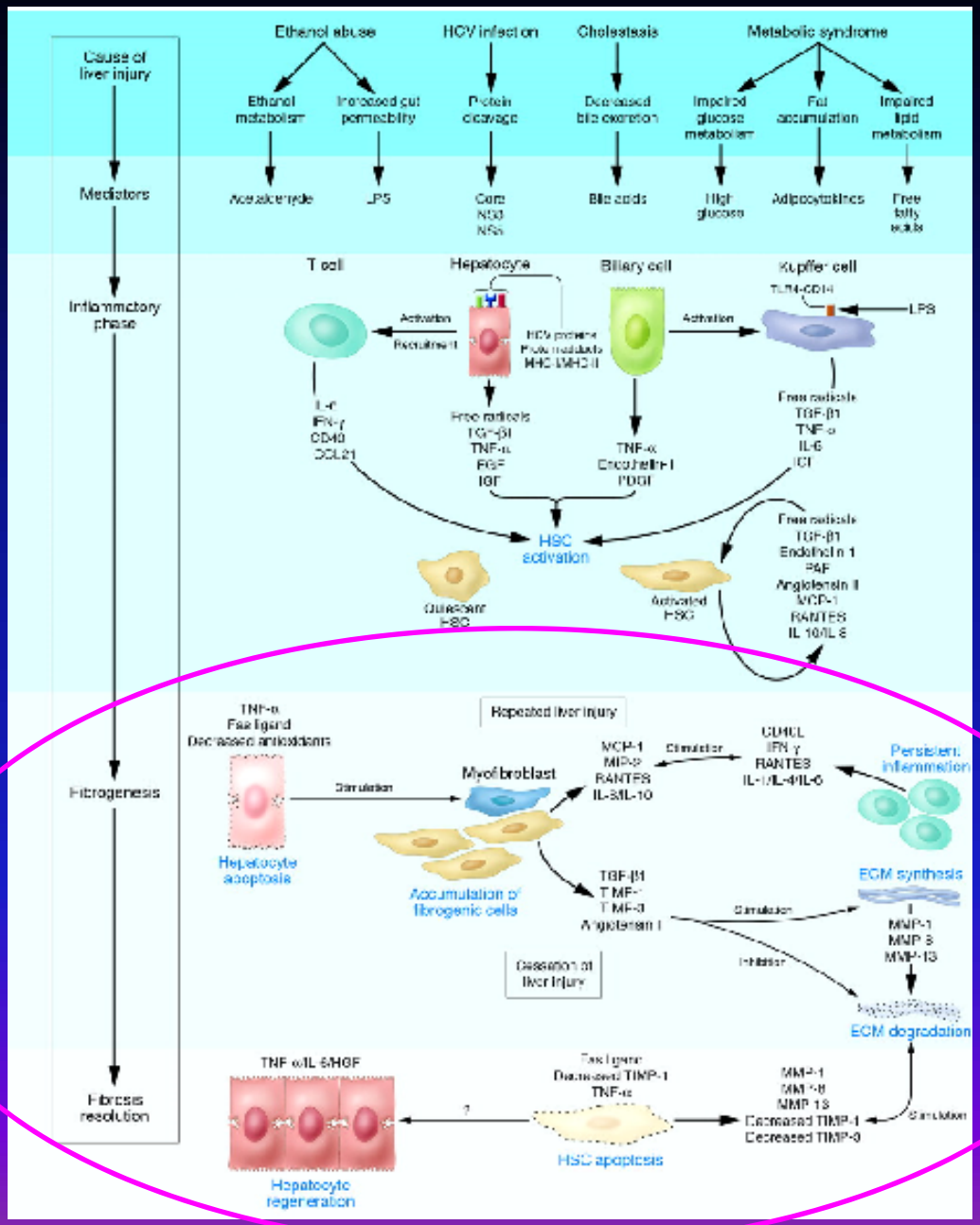


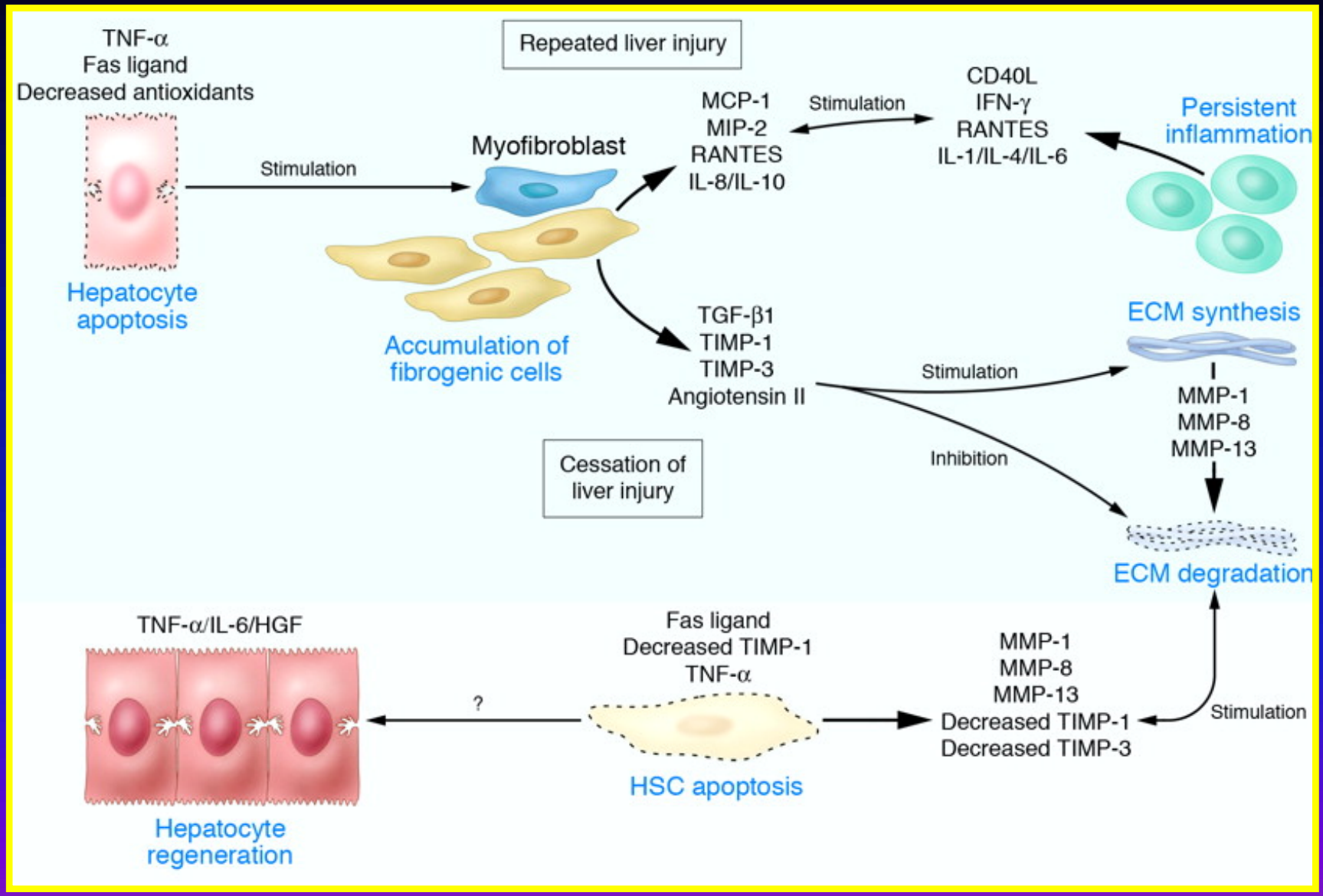
Figure 5 Kaplan–Meier survival curves in the subset of patients with the most severe degrees of cirrhosis (Laennec grade 4C) on biopsy according to drinking status at 30 days post-biopsy ($P < 0.02$)

Alcohol Intake 7 - 60 gr/day

Verrill et al, Addiction 2009

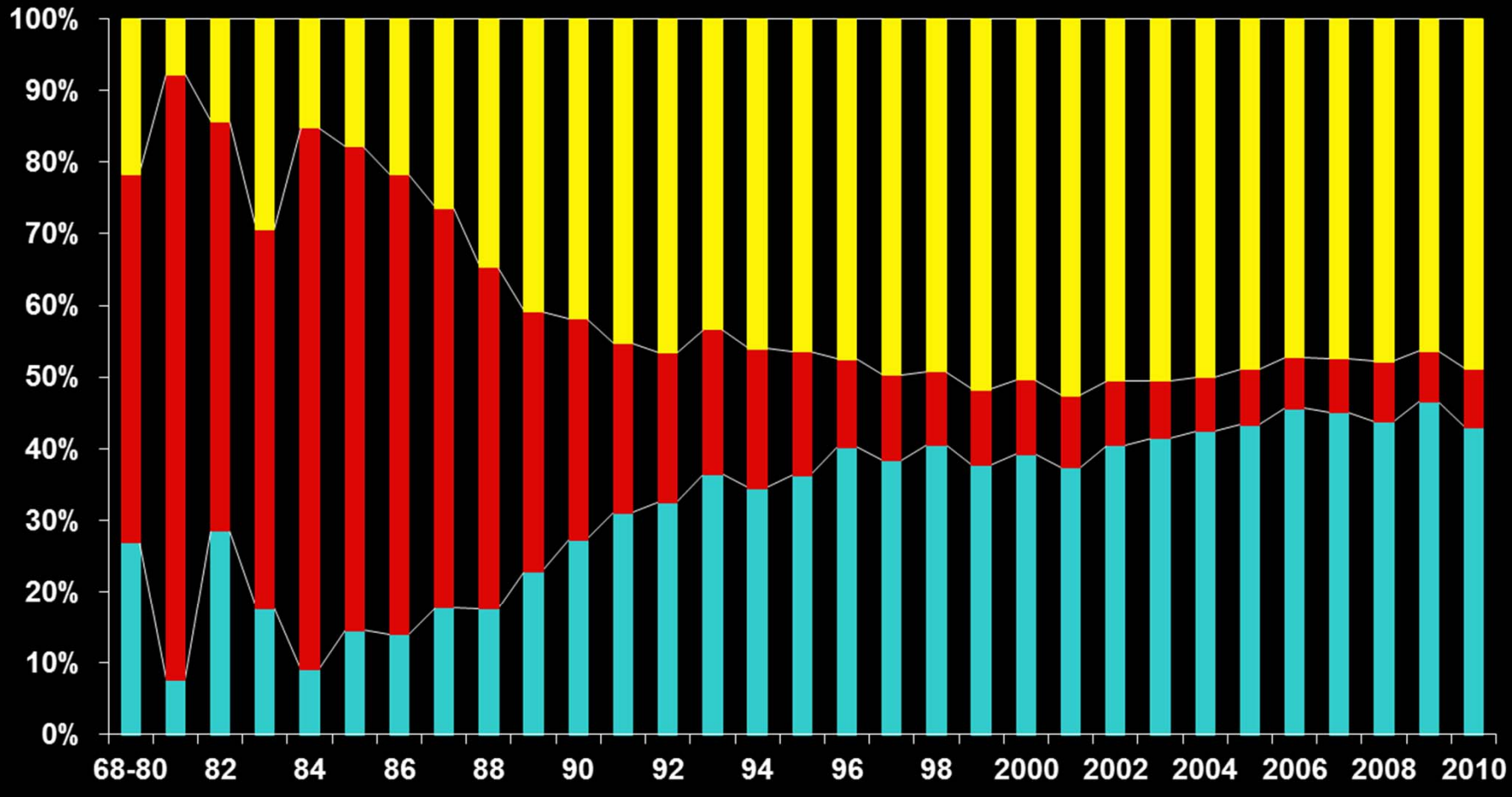


R. Bataller, 2005

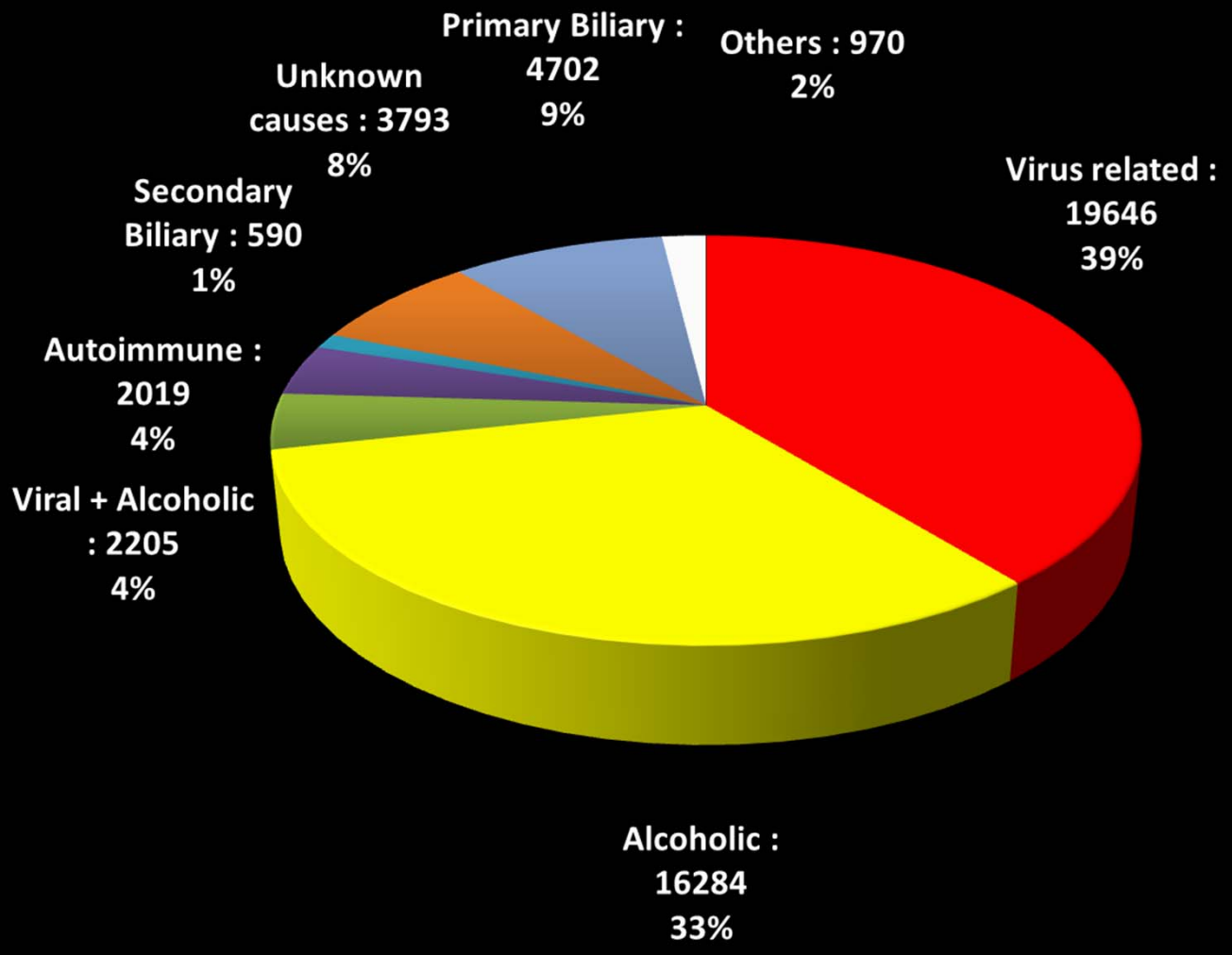


R. Bataller, 2005

Evolution of Indications for Cirrhosis in Europe



Liver Transplantation in Europe
Indications of Cirrhosis
01/1988 - 12/2010



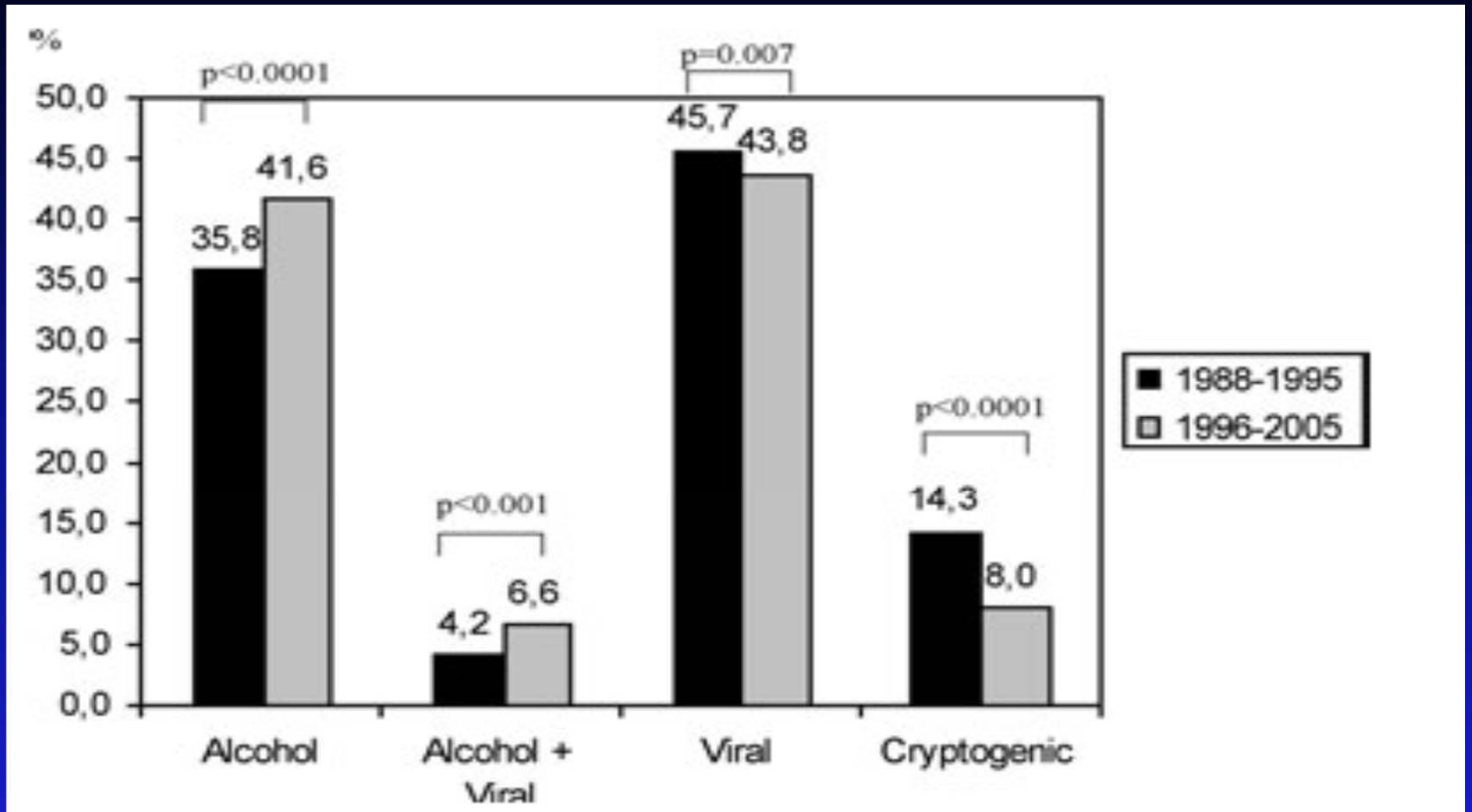


Figure 1: ELTR Indication to liver transplantation in periods 1988–1995 and 1996–2005.

Burra P et al, Am J Transpl 2010

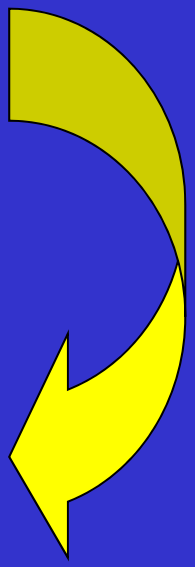
TRAPIANTO DI FEGATO PER EPATOPATIA ALCOL-CORRELATA

Fattori di rischio rispetto ad epatopatie ad altra eziologia

- Comorbidità (neoplasie, cardiopatia, neuropatia, nefropatia, pancreatite, …)
- Astinenza (regola dei 6 mesi)

PROBLEMI ETICI
TRAPIANTO DI FEGATO e ALCOL

- **Patologia “auto-inflitta”**
- **Opinione pubblica**
- **Difficoltà nel definire criteri predittivi di recidiva**
  - **» Rischio di scarsa “compliance”**



CARENZA DI DONATORI D’ORGANO

STUDIO HONG KONG

281 intervistati sulla utilità del Trapianto di Fegato

75%

per chi affetto da **malattia naturale**

ma non per chi presenta **malattia epatica autoinflitta**

Chang, Hong Kong Medical Journal 2006

Assessing priorities for allocation of donor liver grafts: survey of public and clinicians

,

Opinione:

- Il 17% di 1.000 persone intervistate tra la popolazione generale
- Il 40% di 200 medici di Medicina Generale
- Il 33% di 100 medici Specialisti in Gastroenterologia

riteneva che

"Il paziente con malattia epatica alcol correlata
e' il candidato meno meritevole per il trapianto di fegato"

Neuberger J Br Med J 1998

Liver Transplant : HCV + vs HCV -

Table 4. Patient Survival of HCV-Positive vs. Subgroups of HCV-Negative Recipients

Group	1 year (95% CI)	3 year (95% CI)	5 year (95% CI)
HCV+	86.4% (85.3–87.5)	77.8% (76.3–79.2)	69.9% (67.3–72.3)
HCV−	87.5% (86.7–88.3)	81.8% (80.7–92.8)	76.6% (74.9–78.2)
Cholestatic[a,b]	91.5% (89.3–93.2)	88.6% (86.0–90.7)	86.1% (82.6–88.9)
Metabolic[a]	86.5% (82.3–89.8)	83.3% (78.5–87.1)	82.4% (77.1–86.5)
HBV	87.4% (83.8–90.2)	79.5% (74.7–83.5)	78.6% (73.5–82.9)
AIH	84.7% (81.2–87.7)	82.2% (78.4–85.5)	76.8% (70.5–81.9)
Cryptogenic	86.3% (84.1–88.2)	80.9% (78.3–83.3)	73.0% (68.2–77.1)
ETOH	86.7% (84.8–88.3)	78.1% (75.6–80.4)	72.0% (68.1–75.5)
HCV+	86.4% (85.3–87.5)	77.8% (76.3–79.2)	69.9% (67.3–72.3)
Malignancy[a]	82.5% (75.9–87.5)	64.1% (54.7–72.0)	51.8% (34.6–66.5)

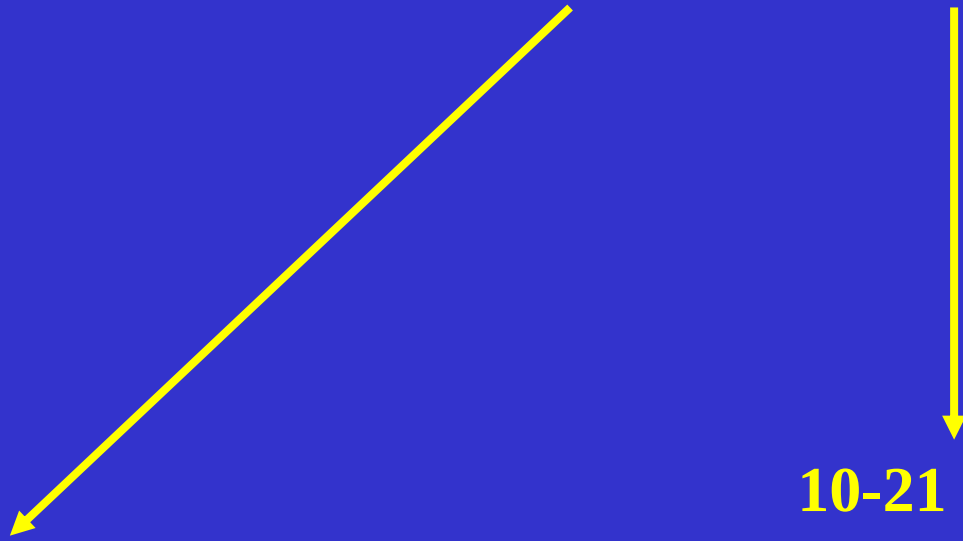
CI, confidence interval; HBV, hepatitis B virus; AIH, autoimmune hepatitis.

[a]$p < 0.05$. This is based on a proportional-hazards model, using all available follow-up time, comparing each of the subgroups to the HCV-positive group.

[b]Cholestatics refers to patients with either primary sclerosing cholangitis or primary biliary cirrhosis.

L Forman Gastroentererology 2002

HCV induced allograft hepatitis and fibrosis/cirrhosis



10-21 % a 5 years dal tx

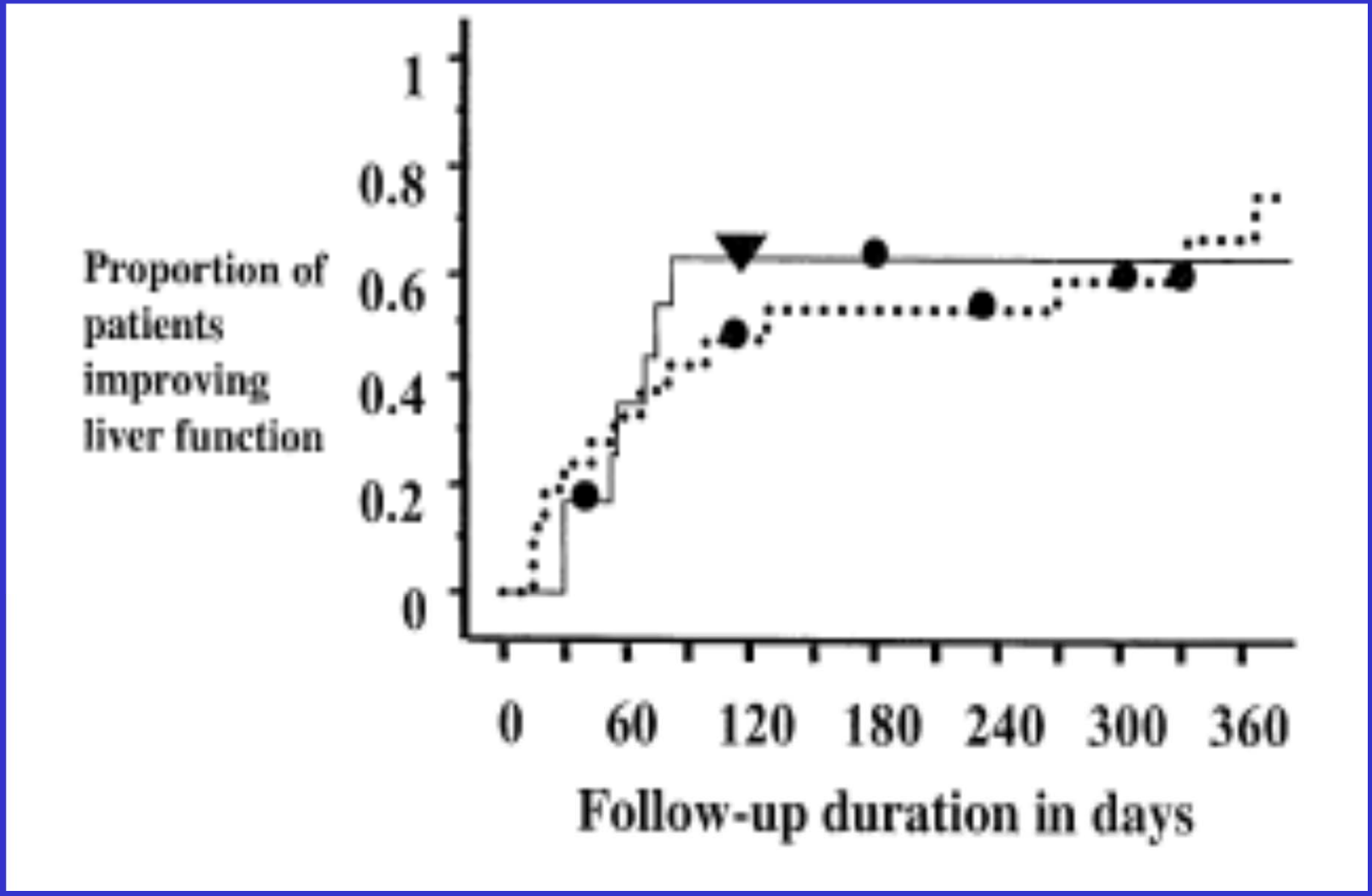
75-80 % a 5 years tx

L Forman Gastroentererology 2002

COMPLICATIONS OF CIRRHOSIS

- ASCITES
- DILUTIONAL HYPONATREMIA
- HEPATORENAL SYNDROME
- BACTERIAL INFECTION
- SPONTANEOUS BACTERIAL PERITONITIS
- HEPATIC ENCEPHALOPATY
- VARICEAL BLEEDING
- PORTOPULMONARY HYPERTENSION
- HEPATOPULMONARY SYNDROME
- HEPATOCELLULAR CARCINOMA

Improving liver function



B. J. Veldt. Journal of Hepatology 2002

MODEL FOR END-STAGE LIVER DISEASE (MELD)

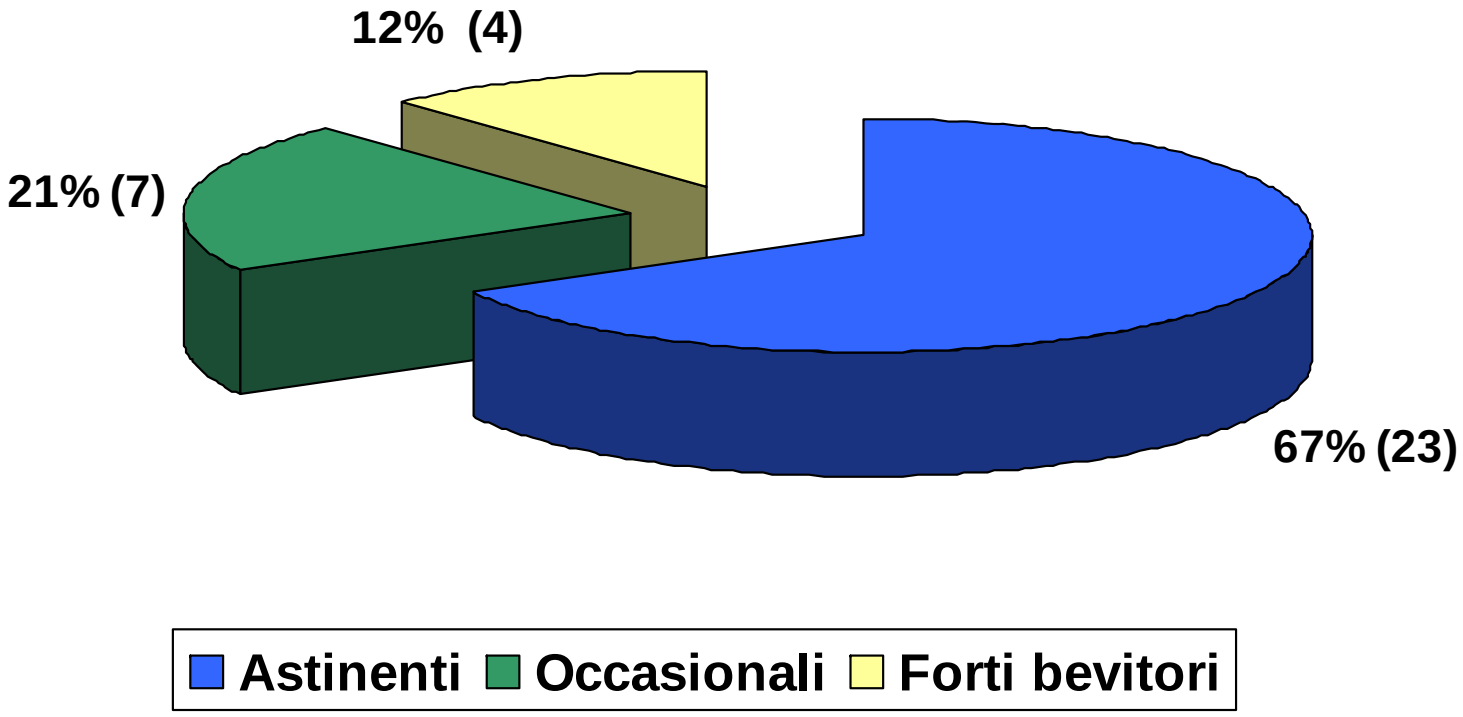
Table 1 Mortality at 3 months in patients hospitalized with liver disease stratified according to MELD score

MELD score	Three-month mortality in hospitalized patients (%)
≥40	100
30–39	83
20–29	76
10–19	27
<10	4

MELD model for end-stage liver disease. Based on Kamath et al. [4]

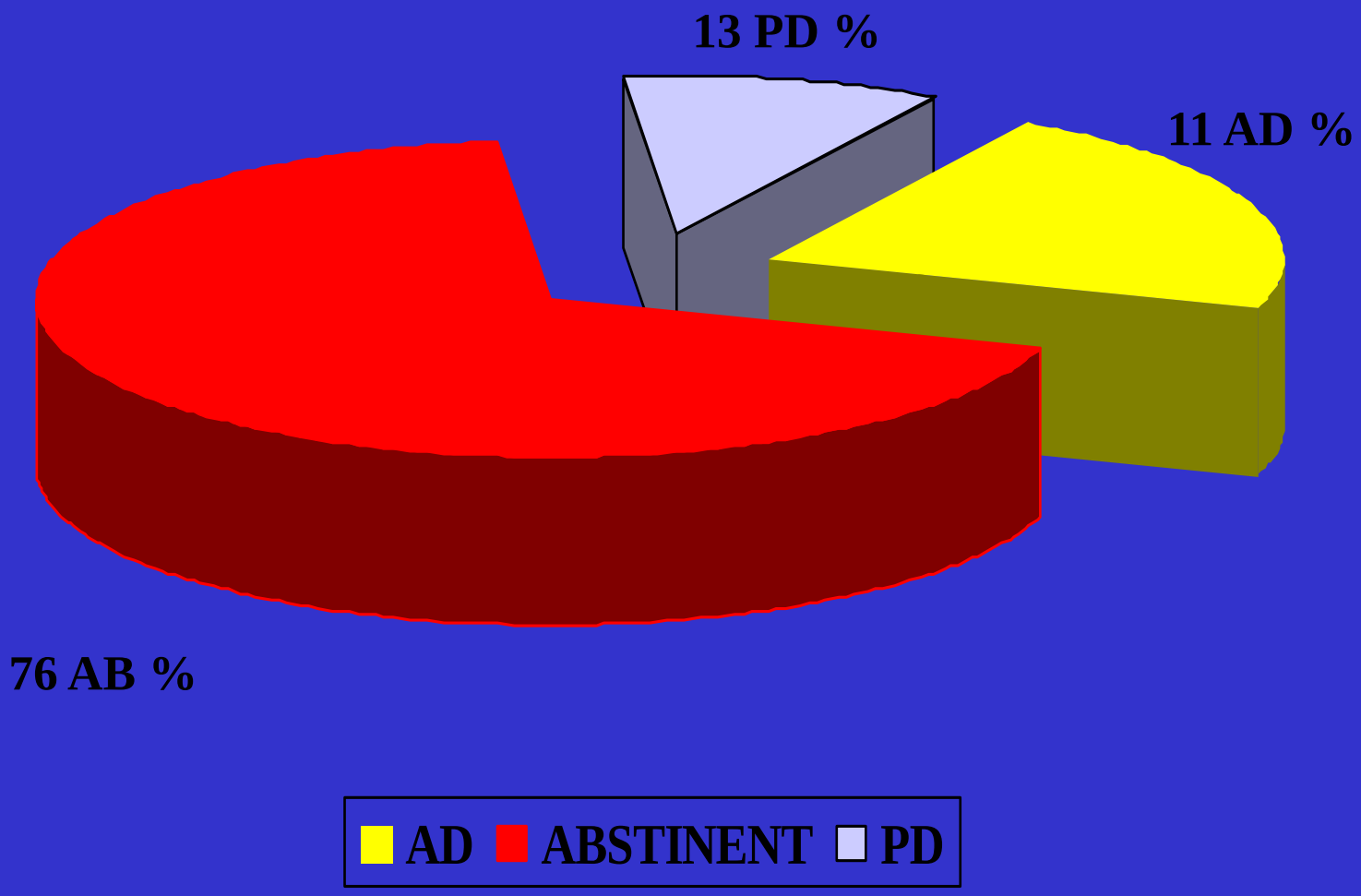
Al Sibae and Cappell, Dig Dis Sci 2011

RECIDIVA DI CONSUMO ALCOLICO DOPO TRAPIANTO DI FEGATO

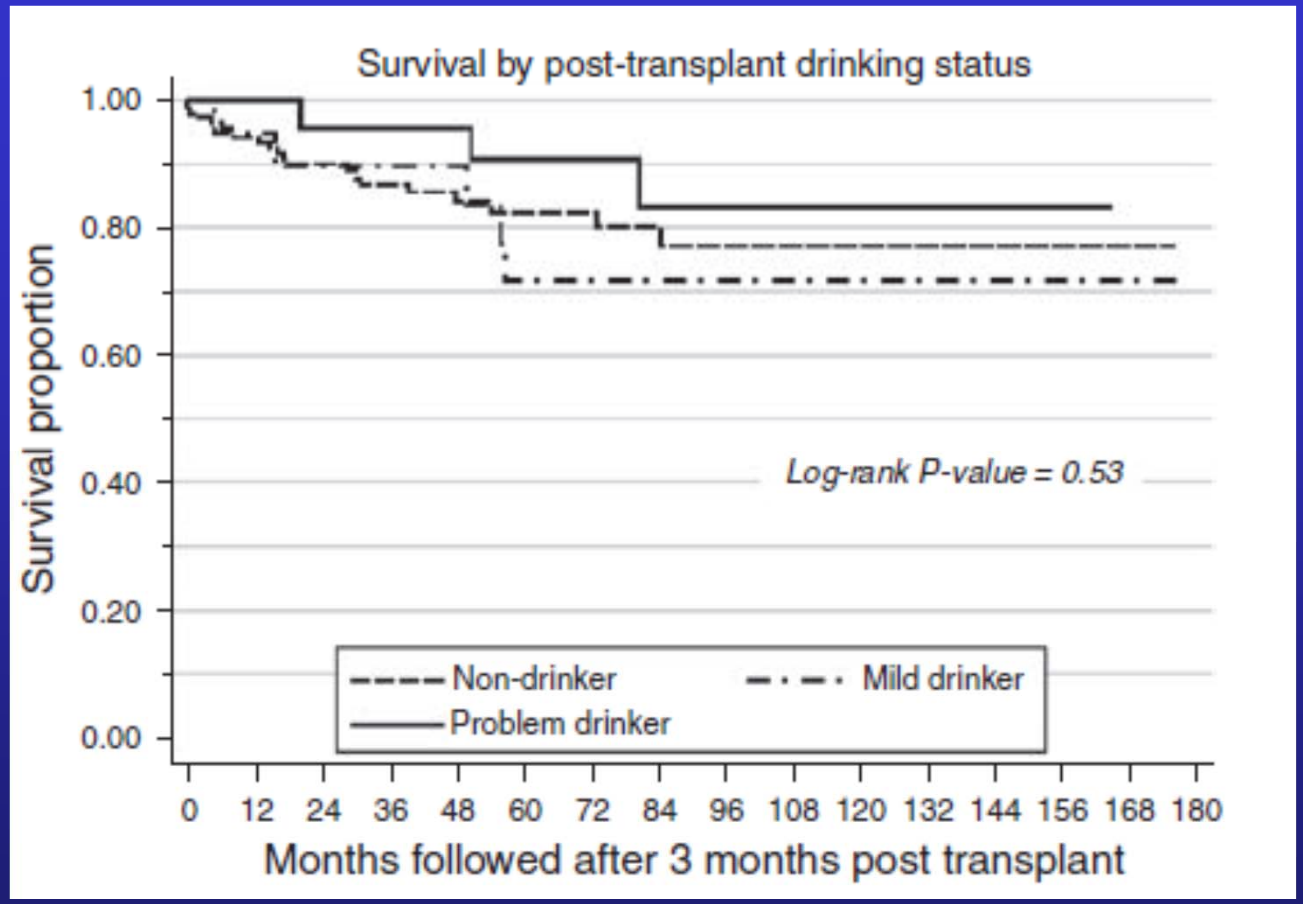


Burra Transpl Int 2000; 13(1): 174-178

RECIDIVA CONSUMO ALCOLICO



Tandon P. Am J Gastroent 2009



Tandon et al, Am J Gastroenterol 2009

Analisi fattori predittivi di recidiva di consumo alcolico dopo trapianto di fegato per patologia epatica alcol-correlata

Authors	Type of study	Patients (N)	Duration of study	Relapse rate	Factors associated with relapse
Berlakovich et al. [9]	retrospective	58	33 months	31%	none
Osario et al. [10]	retrospective	43	21 months	19%	Abstinence < 6 months
Lucey et al. [11]	retrospective	59	63 months	34%	None
Foster et al. [12]	retrospective	63	49.3 months	21%	Associated drug use, drunken driving, club member, life insurance policy, number of alcohoic sisters
Tang et al. [13]	retrospective	56	24 months	48%	None
Pageaux et al. [14]	retrospective	53	42 months	32%	Abstinence < 6 months, age
Conjeevaram et al. [15]	retrospective	68	42 months	—	Histological signs of alcoholic hepatitis on explant
Platz et al. [16]	retrospective	167	ND	26%	Abstinence < 6 months, female, unstable personality, unfavorable environment
Burra et al. [17]	prospective	51	40 months	33%	Patient and/or family awareness of alcoholism
Pereira et al. [18]	retrospective	47	ND	50%	Age at onset of regular consumption, age at onset of excessive intake, duration of abstinence before transplantation
Gisch et al. [19]	prospective	61	62.5 months	20%	Personality disorder, lack of compliance
Bellamy et al. [20]	retrospective	123	7 years	13%	Duration x quantity of alcohol

Miguet, Gastroenterol Clin Biol 2004

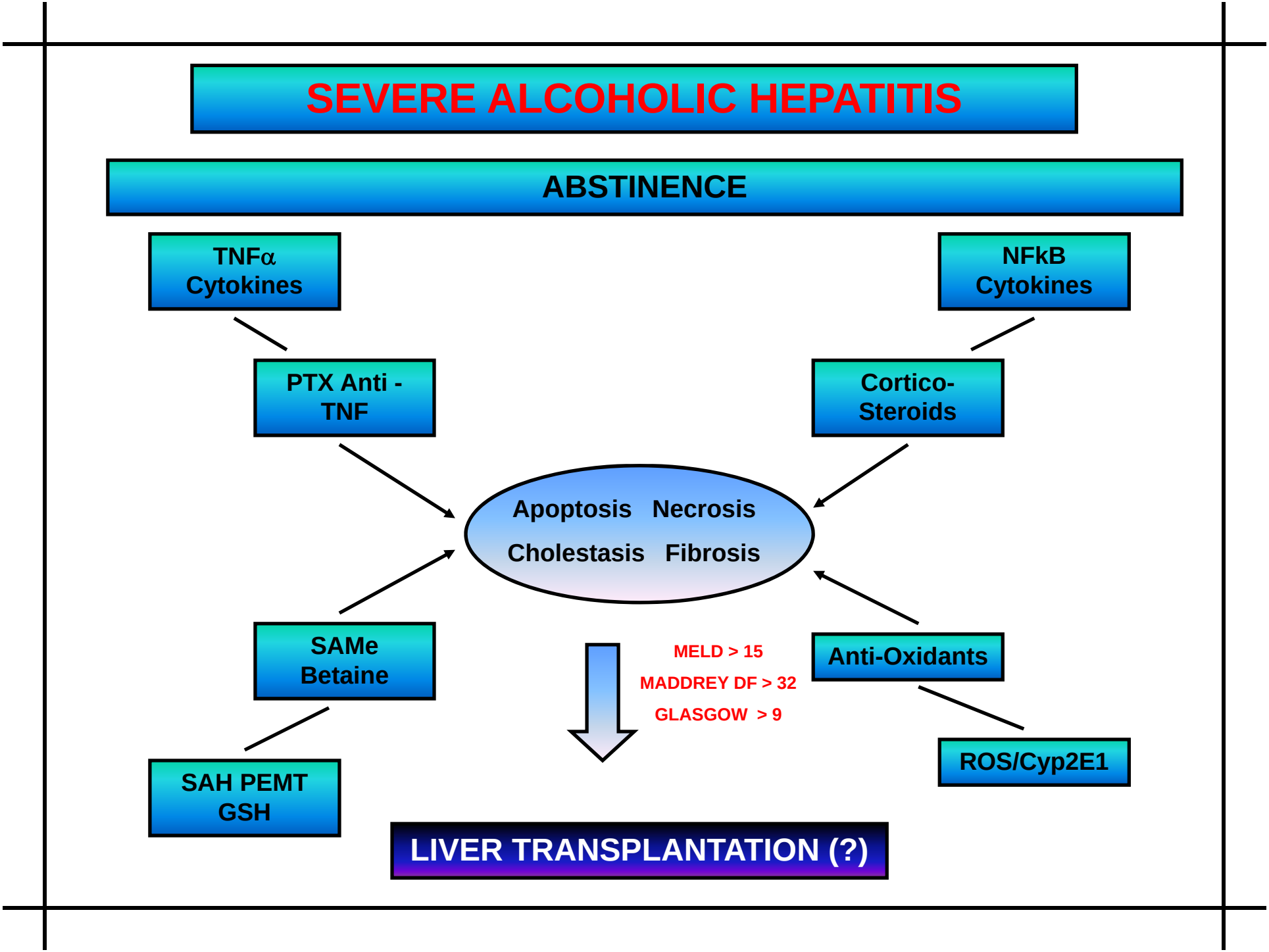
EPATITE ALCOLICA ACUTA

La manifestazione clinica copre un largo spettro di segni e sintomi che vanno dall'ittero asintomatico a forme piu' severe caratterizzate dalla combinazione di encefalopatia, febbre, astenia, coagulopatia, leucocitosi

Wells JT, Liver Transplantation 2007

Mortalita' a 30 giorni: 35-40% dei casi; a 6 mesi: 70% dei casi

Day CP, Liver Transplantation 2007; Burroughs AK, Int Hepatol 2012


SEVERE ALCOHOLIC HEPATITIS
ABSTINENCE
TNFα Cytokines
NFkB Cytokines
PTX Anti - TNF
Cortico-Steroids
Apoptosis Necrosis
Cholestasis Fibrosis
SAMe Betaine
Anti-Oxidants
MELD > 15
MADDREY DF > 32
GLASGOW > 9
SAH PEMT GSH
ROS/Cyp2E1
LIVER TRANSPLANTATION (?)

COMPLICATIONS OF CIRRHOSIS

- ASCITES
- DILUTIONAL HYPONATREMIA
- HEPATORENAL SYNDROME
- BACTERIAL INFECTION
- SPONTANEOUS BACTERIAL PERITONITIS
- HEPATIC ENCEPHALOPATY
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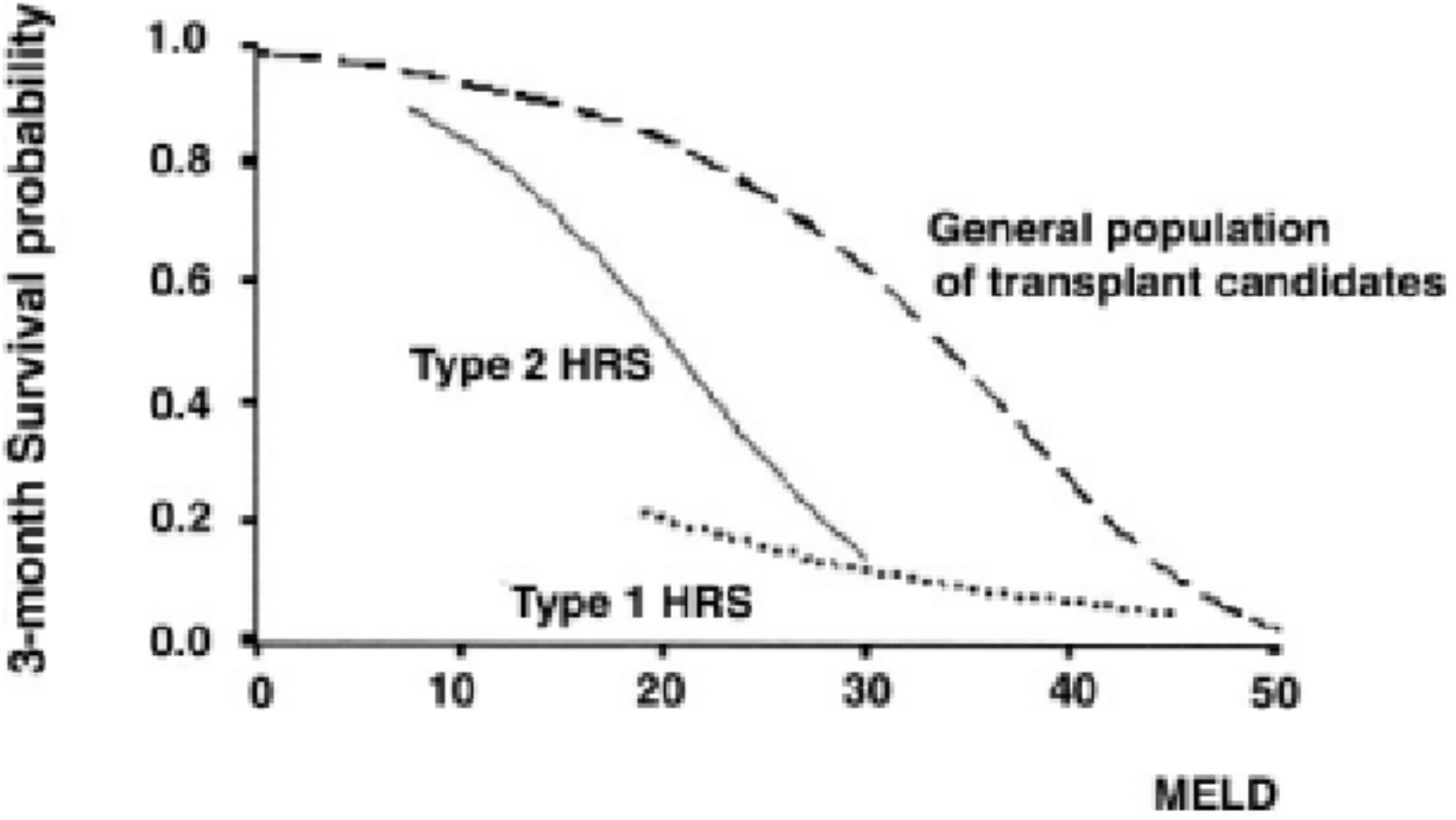


C. Alessandria et al., 2005

COMPONENTS OF SCORING SYSTEMS USED TO ASSES PROGNOSIS IN ALCOHOLIC HEPATITIS

	Poor Prognosis
Maddrey ' s Discriminant Function	> 32
MELD SCORE (Model for End Stage Liver Disease)	> 18
GLASGOW SCORE	> 8
LILLE SCORE	> 0.45

MR Lucey et al,N Engl J Med 2009

AASLD , Hepatology 2010

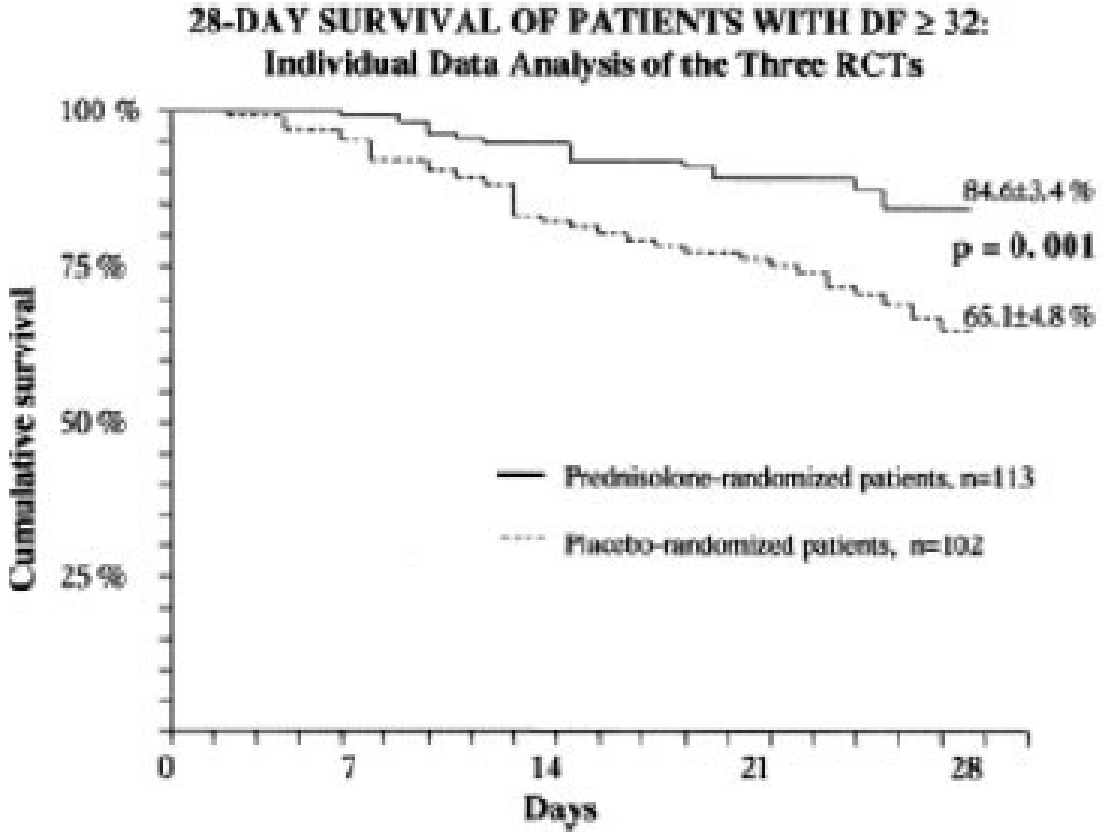


Figure 3. Twenty-eight-day survival in patients with discriminant function >32 treated with corticosteroids or placebo. From Mathurin P, Mendenhall CL, Carithers RL Jr, Raymond MJ, Maddrey WC, Garstide P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis AH: Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 2002;36:480-487.

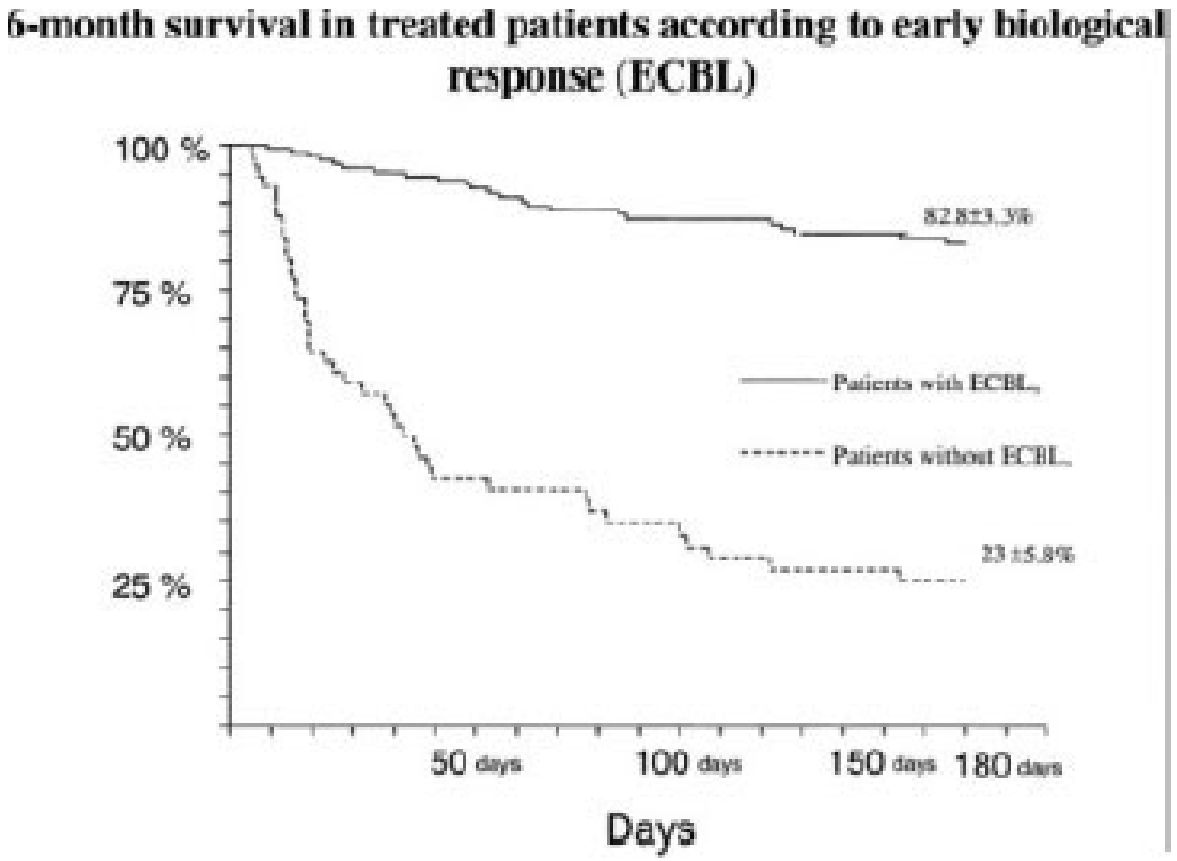
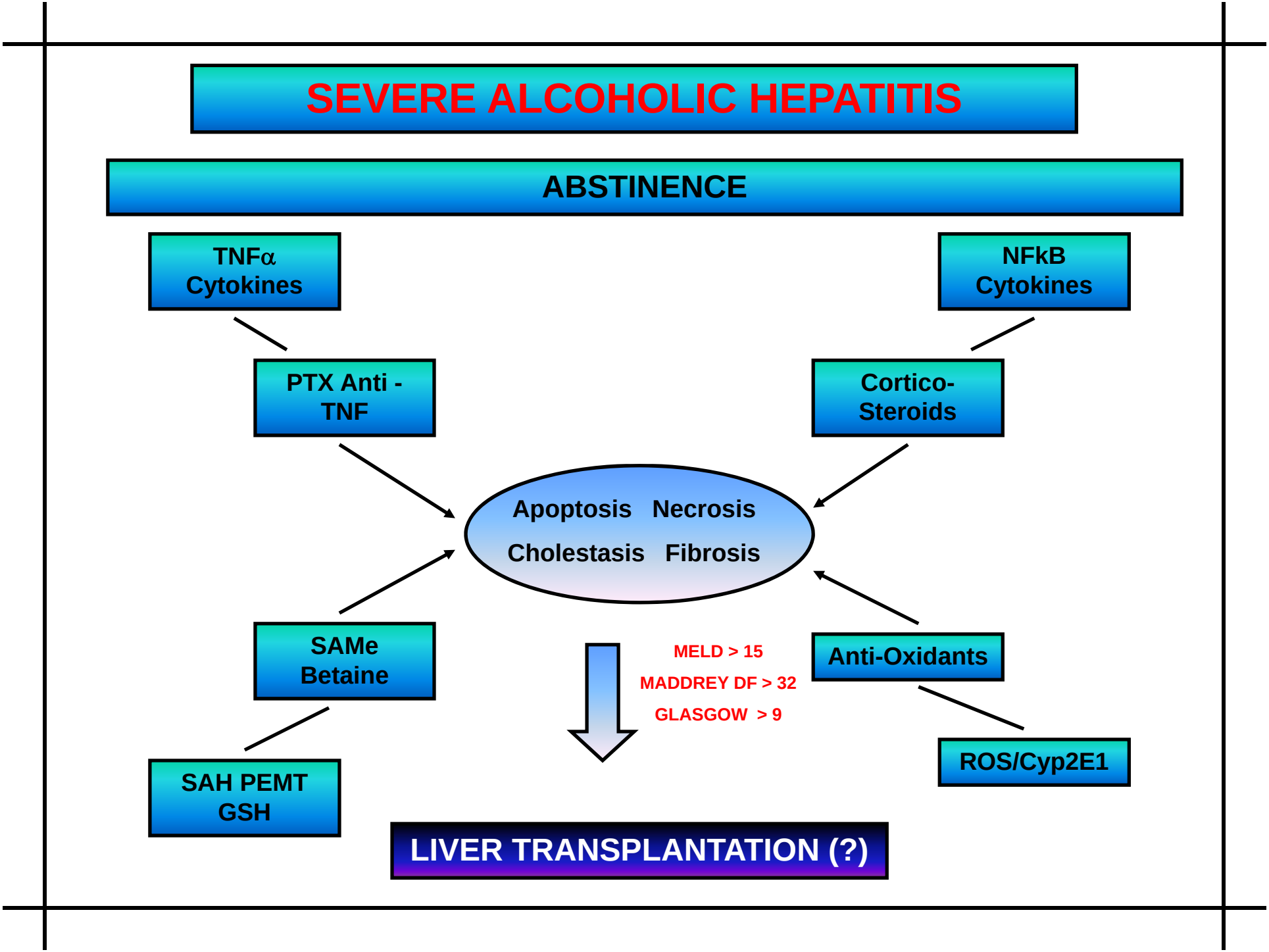


Figure 4. Six-month survival in patients treated with corticosteroids according to early biological response (ECBL). From Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003;38:1363-1369.


SEVERE ALCOHOLIC HEPATITIS
ABSTINENCE
TNFα Cytokines
NFkB Cytokines
PTX Anti - TNF
Cortico-Steroids
Apoptosis Necrosis
Cholestasis Fibrosis
SAMe Betaine
Anti-Oxidants
MELD > 15
MADDREY DF > 32
GLASGOW > 9
SAH PEMT GSH
ROS/Cyp2E1
LIVER TRANSPLANTATION (?)

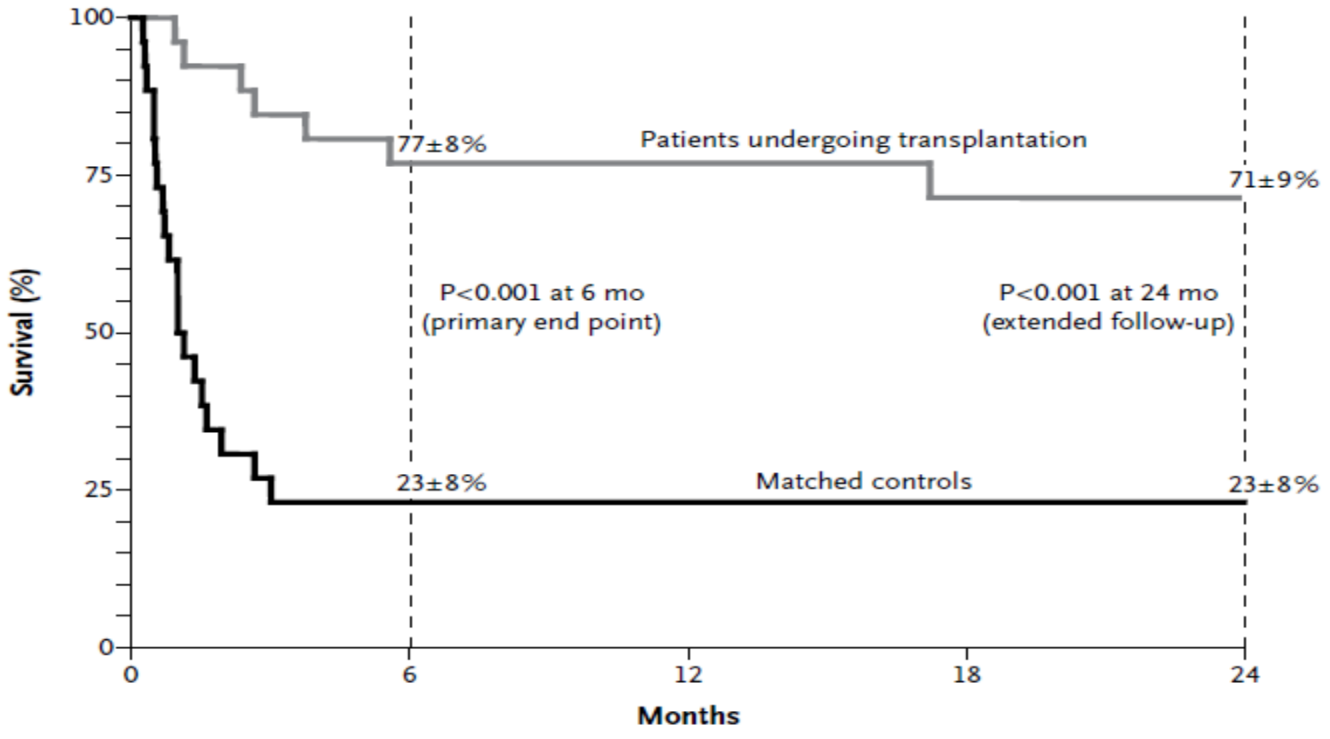
EARLY TRANSPLANTATION OF NON RESPONDERS TO STEROIDS IN SEVERE ALCOHOLIC HEPATITIS

6 – month survival was higher in the transplanted – non responders than in non transplanted –non responders controls :

83.3 +/- 8.7% vs 44.4 + /-11.7% p= 0.009

alcohol relapse: none was observed at 1 year, and only 1 relapsed at 917 days (3 units/week)

Shawcross and O' Grady , Lancet 2010



No. at Risk

Patients undergoing transplantation	26	20	15	14	13
Matched controls	26	6	6	5	4

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

Mathurin et al, NEJM 2011

ASTENSIONE COME UNICO PARAMETRO ?

End Stage Liver Disease con MELD > 20 senza recupero clinico-laboratoristico dopo circa 3 mesi di astensione

Epatite Alcolica Acuta Severa (DF > 32) non responder alla terapia medica o con complicanze (HRS) che ne peggiorano ulteriormente la prognosi

Consensus Conference – American Association for the Study of Liver Disease

A duration of 6 months of abstinence before liver transplantation should no longer be the definite rule and should not be considered the determining factor for graft access;

The term (pre-transplant) recurrence seems incorrect: it would be better to consider it as a relapse in alcohol dependence in order to differentiate it from isolated alcohol consumption;

An episode of alcohol intoxication does not necessarily translate into relapse;

Societal attitudes towards the patient must change. The alcoholic patient should be considered as suffering from a double pathology, both hepatic and alcoholic

Liver Transplantation, 2005

THE SEARCH FOR GENETIC RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

Genetic variationmodulating addiction to alcohol

Genetic variation of alcohol-metabolising enzymes

Genetic variations involved in oxidative stress

Genetic variations controlling hepatic lipid storage

Genetic polymorphisms modulating endotoxin inflammation

Polymorphic variants of fibrosis-associated genes

Stickel and Hampe, Gut 2011

Recidivism (risk use) not necessarily reflects alcoholic liver disease. The dissociation may be because the transplanted liver changes the genetic susceptibility ……..

Burroughs, International Hepatology 2012

… reported rates of alcohol relapse range from 11.5% to 49%, although this fact was rarely considered a reason for graft failure in recipients with ALD.

Graft dysfunction related to relapse ranged from 0% to 17% although death related to relapse ranged from 0% to 5%

Cuadrado et al, Liver Transplantation 2005; DiMartini et al, Liver Transplantation 2006; De Gottardi et al, Arch Intern Med 2007; Burra P et al, Am J Transpl 2010; Lucey, Liver Transplantation 2011;

Table 7 Results in the literature on liver transplantation for alcoholic cirrhosis

Reference	*Period*	*Number*	*Follow up (months)*	*Survival (%)*				*Long term survivors*	*Recidivism (%)*	*Graft dysfunction related to recidivism (%)*	*Deaths related to recidivism (%)*
				1 year	*2 year*	*3 year*	*5 year*				
Bird and coworkers[3]	1980–1989	24	ND (4–84)	66				18	22	ND	0
Kumar and coworkers[2]	1982–1988	73	ND	74		62		52	11.5	2	2
Knechtle and coworkers[4]	1984–1990	41	ND	83			71	30	13	0	0
Berlakovitch and coworkers[7]	1982–1993	58	33	71			63	44	31	16	4.5
Osorio and coworkers[8]	1988–1991	43	21	100				37	19	ND	0
Raakow and coworkers[9]	1988–1994	78	25	96			85	ND	22	ND	2.5
Gerhardt and coworkers[10]	1985–1991	67	47		67 overall			41	49		4.4
Foster and coworkers[18]	1986–1994	88	49	79	75			63	22	17	5
Lucey and coworkers[11]	1987–1991	59	63	80			77	50	34		
Anand and coworkers[17]	1987–1994	39		79			79		13		
Gish and coworkers[6]	1988–1991	29	24	93				29	21	ND	0
Doffoel and coworkers[5]	1985–1991	75	29	80		68		57	26		
Pageaux and coworkers	1989–1994	53	42	75	69	67	62	47	32	4	2

ND, not determined.

Pageaux et al, Gut 1999

The focus on recidivism due to alcohol, rather than survival as the primary outcome after transplantation for alcoholic cirrhosis has been challenged

Burroughs, Int Hepatol 2012

Shawcross and O'Grady, Lancet 2010

Cause di morte dopo trapianto di fegato per cirrosi alcol-correlata

Patient	Transplant indication	Alcohol relapse	Cause of death	Survival (mo)	*Months after alcohol relapse
1	ALD	Yes	Metastatic dissemination of laryngeal epidermoid carcinoma	72	25
2	ALD	Yes	Sudden death	98	59
3	ALD	No	Hepatic metastases of pancreatic adenocarcinoma	102	—
4	ALD	Yes	Bone metastases of squamous pharyngeal carcinoma	95	36
5	ALD	No	Invasive bladder carcinoma	31	—
6	ALD	Yes	Acute myocardial infarction	93	48
7	ALD	Yes	Biliary sepsis	72	63
8	ALD	Yes	Acute stroke	91	36
9	ALD	No	Biliary sepsis	70	—
10	ALD	No	Acute myocardial infarction	90	—
11	ALD and HCC	Yes	Cerebral hemorrhage	14	10
12	ALD and HCC	No	Relapse of HCC with metastatic dissemination	57	—

Abbreviations: ALD, alcoholic liver disease; HCC, hepatocellular carcinoma.
* Time in months from alcohol relapse to the diagnosis of the clinical event that caused death.

Cuadrado Liver Transplantation 2005;4:420-426

Aderenza alle prescrizioni mediche in pazienti con cirrosi alcol e non alcol-correlata

D. Canova & G. Germani, AISF 2007

	Alcol (n=67)	Non Alcol (n=67)	
			p
Mancata assunzione della terapia			
Si (qualche volta, spesso)	**31 (47%)**	**40 (58.8%)**	***n.s.***
No	36 (53)	27 (41.1)	
Assenza visite mediche			
Si (qualche volta, spesso)	**8 (11.7%)**	**8 (11.7%)**	***n.s.***
No	59 (88.2)	59 (88.2)	
Mancata esecuzione esami richiesti			
Si (qualche volta, spesso)	**6 (8.8%)**	**14 (20.5%)**	***n.s.***
No	61 (91.1)	53 (79.4)	

Referral for Consideration Liver Transplantation

Refer patients with decompensated liver disease for assessment for liver transplantation if they still have decompensated liver disease after best management and three months' abstinence from alcohol…

Swain et al., British Medical Journal 2010

ABSTINENCE BEFORE TRANSPLANTATION

Many transplant program (85%) in the United States and Europe require 6 mo of abstinence before transplantation

«… absence of enough evidence to support the 6 mo sobriety.
It is uncleare wheter this is an effective predictor
for post transplant abstinence or simply
a method of consistent selection – popular with insurance companies»

Varma et al, World Journal of Gastroenterology 2010

CIRROSI EPATICA ALCOL CORRELATA

Molto frequente nei contesti ospedalieri (circa il 50% dei decessi dei paz. cirrotici e' alcol correlato)

(il 95% non viene valutato per trapianto e nel 40% dei casi di HCV/HBV consumo dannoso di alcol sottovalutato)

Eccellente condizione clinica da trapianto con sopravvivenza superiore alle altre condizioni

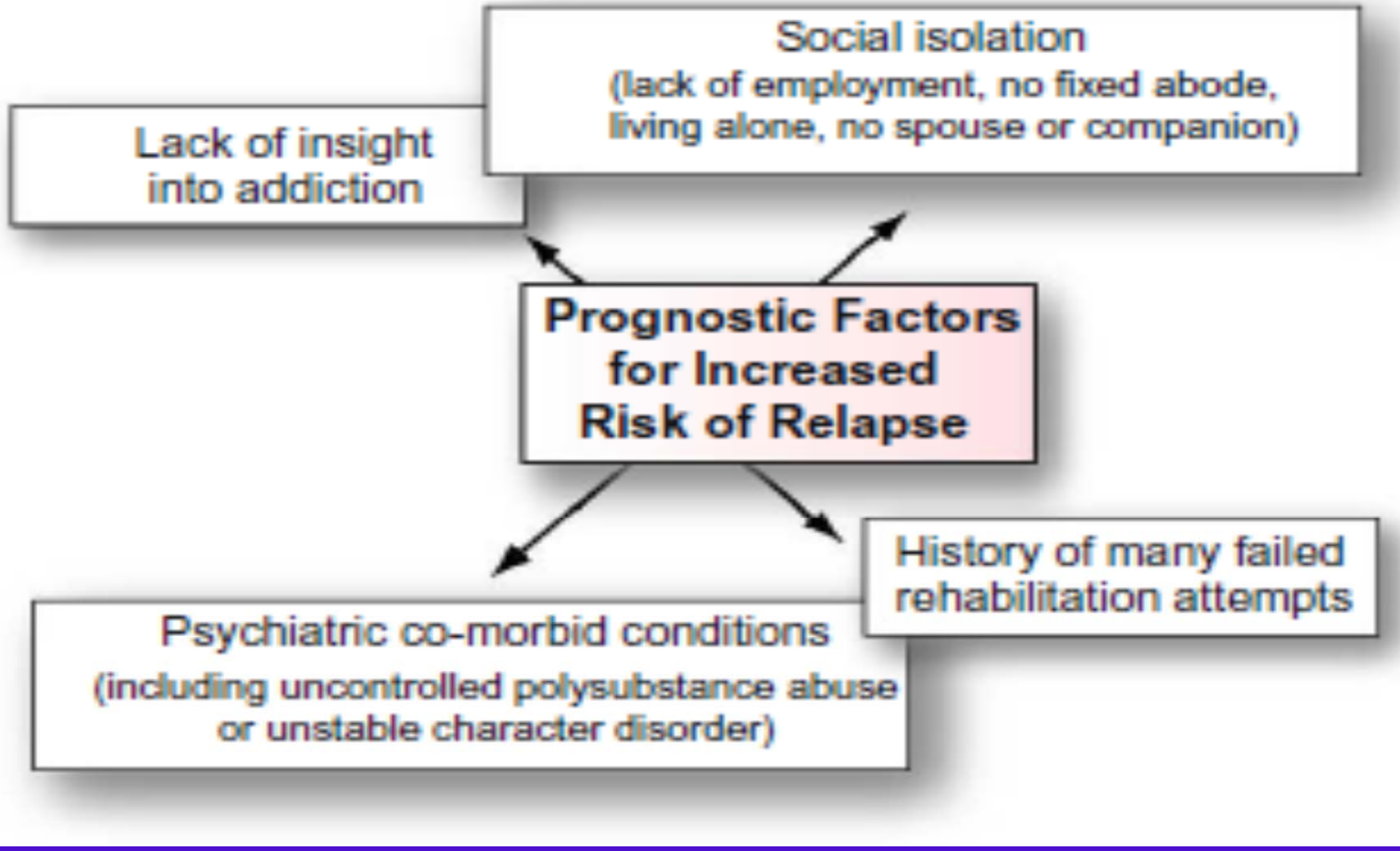
E' NECESSARIO UN CAMBIAMENTO

Rivalutazione del timing trapiantologico

Attivita' interdisciplinare personalizzata

Nuovo modo di lavorare per raggiungimento astensione – follow-up dell'astensione (sobrieta') con coinvolgimento attivo delle Associazioni di auto-mutuo-aiuto

Table 2. Prognostic factors for increased risk of relapse.



Dureja and Lucey, J Hepatol 2010

RISK SCORE

Severita' alcoldipendenza

Presenza di altre dipendenze

Accettazione del problema da parte del candidato e dei familiari

Aderenza al percorso assistenziale

Assenza di disordini psichiatrici concomitanti

Stabilita' e supporto sociale (famiglia, amici, lavoro)

Presenza di figli

Frequenza ai gruppi di auto-mutuo-aiuto

HBAR test (high risk alcoholism relapse); SCL 90 Score

Periodo di astensione (da ricoverato? a casa ? farmaci anticraving?)

Pfitzmann et al, Liver Transplant 2007; Kotlyar et al, Am J Gastroenterol 2008;
Pilling et al, BMJ 2010; Burra P et al, Am J Transpl 2010; Brown, NEJM 2011;
Testino et al, DLD 2012, in press; Burroughs, Int Hepatol 2012

Alcoholic Hepatitis and Liver Transplantation: Is an Abstinence of Six Months Necessary?

Gianni Testino and Paolo Borro

Department of Specialist Medicine, S. Martino Hospital, Genova, Italy

Corresponding author: Prof. Gianni Testino, Padiglione 10, Piazzale R. Benzi 10, Ospedale San Martino, 1632 Genova, Italy; Tel.: 0039-10-555-6733; E-mail: gianni.testino@hsanmartino.it

To the Editor,

Forty-four percent of all deaths from liver disease are attributed to alcohol (1). Alcoholic liver disease (ALD) is the second most common diagnosis among patients undergoing liver transplantation (LT) in Europe and the Unites States. The outcome for patients transplanted for ALD is at least as good as that for most other diagnoses and better than that for HCV (2).

Forman *et al.* (3) evidenced a 5 year survival of 69.9% of HCV positive recipients and of 72% in HCV negative recipients transplanted for ALD. In HCV recipients, fibrosis/cirrhosis was present in 10-21% five years from LT. Reported rates of alcohol relapse ranged from 11.5-49%, although this fact was rarely considered a reason for graft failure in recipients with ALD. Graft dysfunction related to relapse ranged from 0 to 17%, although deaths related to relapse ranged from 0% to 5% (4). More recently, Tandon *et al.* (5) evidenced the risk of post-transplant problem drinking in 13% of cases. In this study there was no survival difference between problem drinkers and non-drinkers.

Alcoholic hepatitis (AH) is a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use. The typical age of presentation is 40 to 60 years (6). The true incidence of AH is unclear. Its prevalence is around 20% among subjects who undergo liver biopsy and it is suspected in 10-35% of hospitalized alcoholics. Less severe forms of acute AH (AAH) frequently respond to alcohol abstinence, whereas the prognosis of severe AAH is poor; up to 40% die within 6 months. Cirrhosis co-exists in over 50% of cases and patients are at risk of variceal bleeding and hepatorenal syndrome (HRS) (7). Severe AAE non-responders to steroids have 6 months survival (approx. 25-30%) and in patients with HRS there is a 3-month mortality of more than 90% unless treated by LT (8-10).

In cases of severe AAH, LT is a therapeutic option in this setting but is rarely used. The reason for denying LT is that it requires abstinence from alcohol for six months before consideration for a transplant. This period is arbitrary and has never been shown to affect survival after LT (1). Even where there is evidence that shorter pre-listing abstinence correlates to shorter time to first drink post-transplant, an optimal period of pre-transplant abstinence remains unclear (2).

In our experience seven patients with severe AAE (Model End Stage Liver Disease over 21 and Maddrey Discriminant Function over 32) and type 1 HRS and non-responders to medical therapy, were submitted to transjugular intrahepatic portosystemic stent shunt (TIPS) and successively transplanted within five months of abstinence (median age 49 years) (unpublished data). None of the patients relapsed after a period of 5 years. Castell *et al.* (11) listed 22 patients for transplantation (median age 47 years) within 15 days of non-response to treatment and 18 patients were transplanted within 9 (range 5-13) days (2 died on the waiting list, 2 recovered). Non-responders to steroids were identified by a Lille score of 0.45 or higher, or worsening of liver function, seven days after presentation. Six-month survival was 83% (compared with 44% in a non-randomised case-matched control group). None of the patients relapsed in the first year although one patient relapsed after 917 days (1 unit/ three times week). Considering that patients who do not recover within the first 3 months of abstinence are unlikely to survive (12) in case of AAH, 3 months of alcohol abstinence may be more ideal than 6 months. Varma *et al.* (2) affirm that there is absence of enough evidence to support the 6 months sobriety. It is unclear whether this is an effective predictor for post transplant abstinence or simply a method of consistent selection popular with insurance companies. Shawcross and O'Grady (12) underlined that a teenager who develops liver failure after a deliberate paracetamol overdose, after taking ecstasy, or after contracting hepatitis B through irresponsible sexual behaviour will have open access to LT. Why should his or her peer who simply drank too much for a few months be treated differently? (12).

A strict application of a period of sobriety as a policy for transplant eligibility is unfair to non-responder patients, as most of them will have died prior to the end of the 6-month sober period (13). In our opinion, in case of severe AAH, subjects with a good social support, without psychotic or personality disorders, should be referred to LT if they still have decompensated liver disease and 3 months of abstinence.

Post-LT, patients with limited comorbidities and good social support should be offered individual cognitive behavioural therapy. Those with significant comorbidities and/or limited social support, should be offered multi-component programmes (multidimensional family therapy, functional family therapy, brief strategic family therapy) (14). The frequency of self-help groups, of which the best known is alcoholics anonymous, is mandatory. We agree with Kodyar *et al.* (15) that the lack of pre-LT abstinence alone should not be a barrier against being listed.

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Characteristics of Alcoholics Attending 'Clubs of Alcoholics in Treatment' in Italy: A National Survey

Olivia Curzio[1], Angela Tilli[2], Lorena Mezzasalma[1], Marco Scalese[1], Loredana Fortunato[1], Roberta Potente[1], Guido Guidoni[2] and Sabrina Molinaro[1,*]

[1]Institute of Clinical Physiology, Italian National Research Council (IFC-CNR), Via Moruzzi 1, Pisa 56124, Italy and [2]Italian Association of Clubs of Alcoholics in Treatment (AICAT), Udine, Italy

*Corresponding author: Tel: +39-50-3152094; Fax: +39-50-3152095; E-mail: molinaro@ifc.cnr.it

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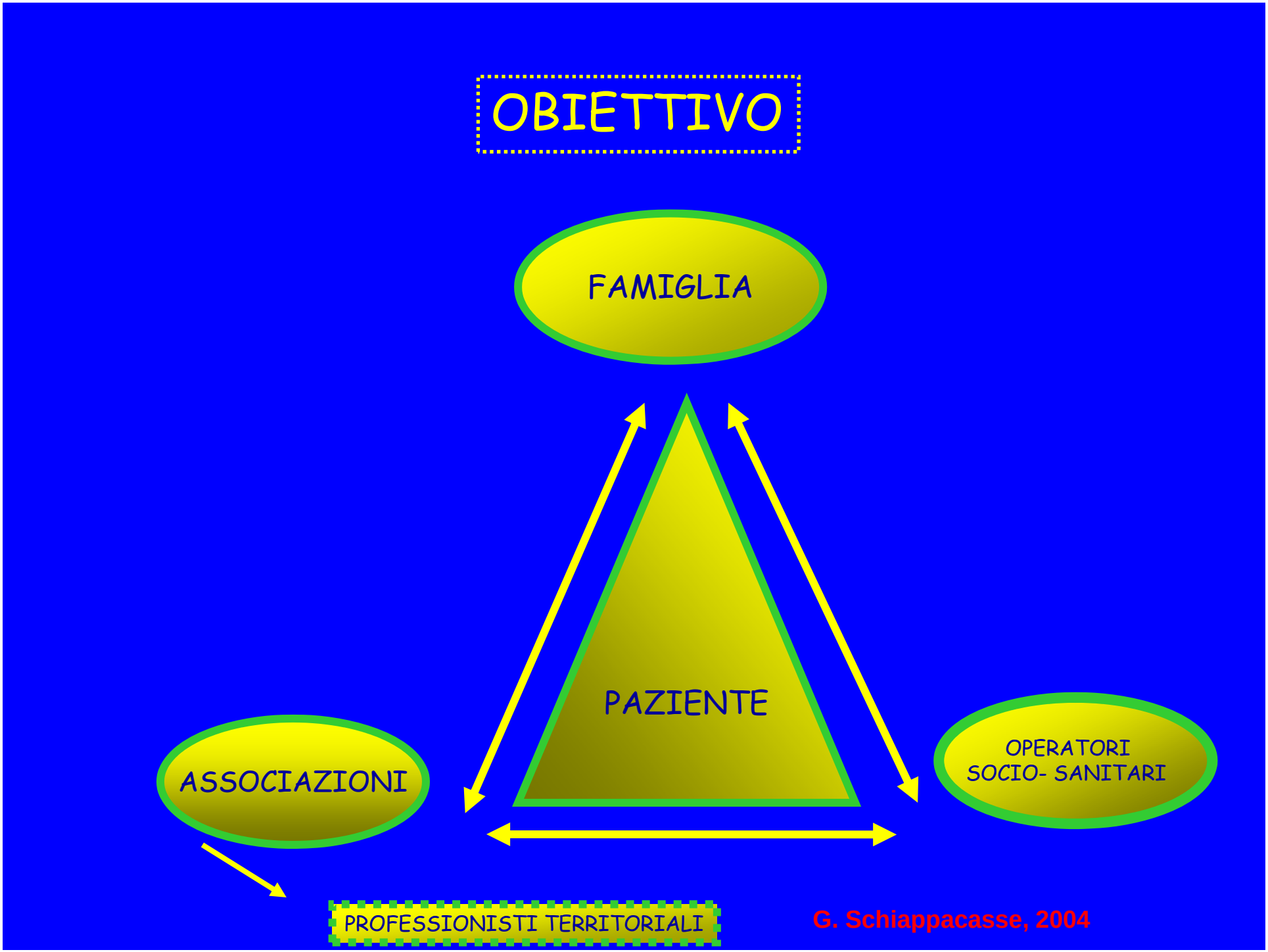
Abstract — Aims: To provide an overview of alcoholics attending a socio-ecological treatment programme [Clubs of Alcoholics in Treatment (CATs)] and to identify factors associated with abstinence and self-perceived improvement in lifestyle. **Methods:** A national sample of 7522 subjects (76% males and 24% females, mean age 53.2 ± 11.3 years ± SD) attending CATs was evaluated using a self-administered questionnaire completed at a weekly meeting in 2006. **Results:** Of participants, >70% reported no alcohol use in the last year and around 90% indicated no use in the previous month, whereas 4% of them declared no alcohol use before club attendance. Abstinence and lifestyle improvement were related positively to the number of years of club attendance but negatively to the presence of other problems in addition to the alcohol-related one. Moreover, being older or female was associated with more likely achievement of abstinence as well as with the perception of a better lifestyle. Finally, attending the club with one or more family members was associated with achievement of better lifestyle. **Conclusion**: These data provide an overview of alcoholics attending the CAT programme and are a first step toward developing a surveillance system. In addition, on the basis of this preliminary picture further research (notably longitudinal studies) can be planned considering this method and its effectiveness.


OBIETTIVO
FAMIGLIA
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PROFESSIONISTI TERRITORIALI
G. Schiappacasse, 2004