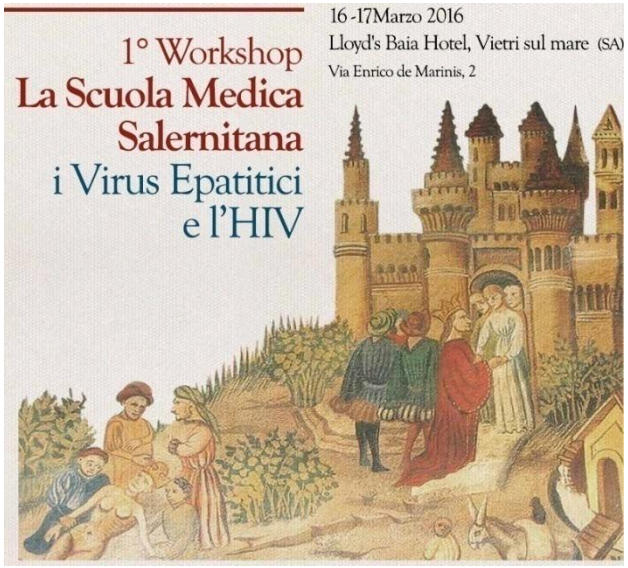

Le manifestazioni extra-epatiche dell'infezione da HCV nell'era dei DAA

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Malattia da HCV
Manifestazioni extraepatiche

Hematologic
- Mixed cryoglobulinemia[1]
- Aplastic anemia[2]
- Thrombocytopenia[2]
- Non-Hodgkin's b-cell lymphoma[2]

Dermatologic
- Porphyria cutanea tarda[1]
- Lichen planus[2]
- Cutaneous necrotizing vasculitis[2]

Renal
- Glomerulonephritis[1]
- Nephrotic syndrome[2]

Endocrine
- Hypothyroidism[2]
- Diabetes mellitus[2]

Ocular
- Corneal ulcer[2]
- Uveitis[2]

Vascular
- Necrotizing vasculitis[2]
- Polyarteritis nodosa[2]

Neuromuscular[2]
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

Autoimmune Phenomena[2]
- CREST syndrome

Neuropsychiatric
- Depression[1]

[1]NIH. *NIH Consens State Sci Statements*. 2002;19:1-46.
[2]Sene D, et al. *Metab Brain Dis*. 2004;19:357-381.

➢**MULTIVIRC group: almeno una MEE-HCV nel 74% dei pz. con infezione da HCV** [1]*Cacoub P.,Poynard T, 1999; Arthritis Rheum,42(10): 2204-12*

Extrahepatic Morbidity and Mortality of Chronic Hepatitis C

Francesco Negro,[1] Daniel Forton,[2] Antonio Craxì,[3] Mark S. Sulkowski,[4] Jordan J. Feld,[5] and Michael P. Manns[6]

Gastroenterology 2015

Manifestations of Chronic Hepatitis C Virus Infection Beyond the Liver

IRA M. JACOBSON,* PATRICE CACOUB,‡ LUIGINO DAL MASO,§ STEPHEN A. HARRISON,‖ and ZOBAIR M. YOUNOSSI¶

Clin Gastroenterol Hep 2010

Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis

Carlo Palazzi, Emilio D'Amico, Salvatore D'Angelo, Michele Gilio, Ignazio Olivieri

W J Gastroenterol 2016

Extrahepatic manifestations of chronic hepatitis C virus infection

Patrice Cacoub, Cloe Comarmond, Fanny Domont, Léa Savey, Anne C. Desbois and David Saadoun

Ther Infect Dis 2016

Extrahepatic manifestations in chronic hepatitis C virus carriers

E Rosenthal[1,2] and P Cacoub[3–6]

Lupus 2015

Hepatitis C virus syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer

Clodoveo Ferri, Marco Sebastiani, Dilia Giuggioli, Michele Colaci, Poupak Fallahi, Alessia Piluso, Alessandro Antonelli, Anna Linda Zignego

W J Hep 2015

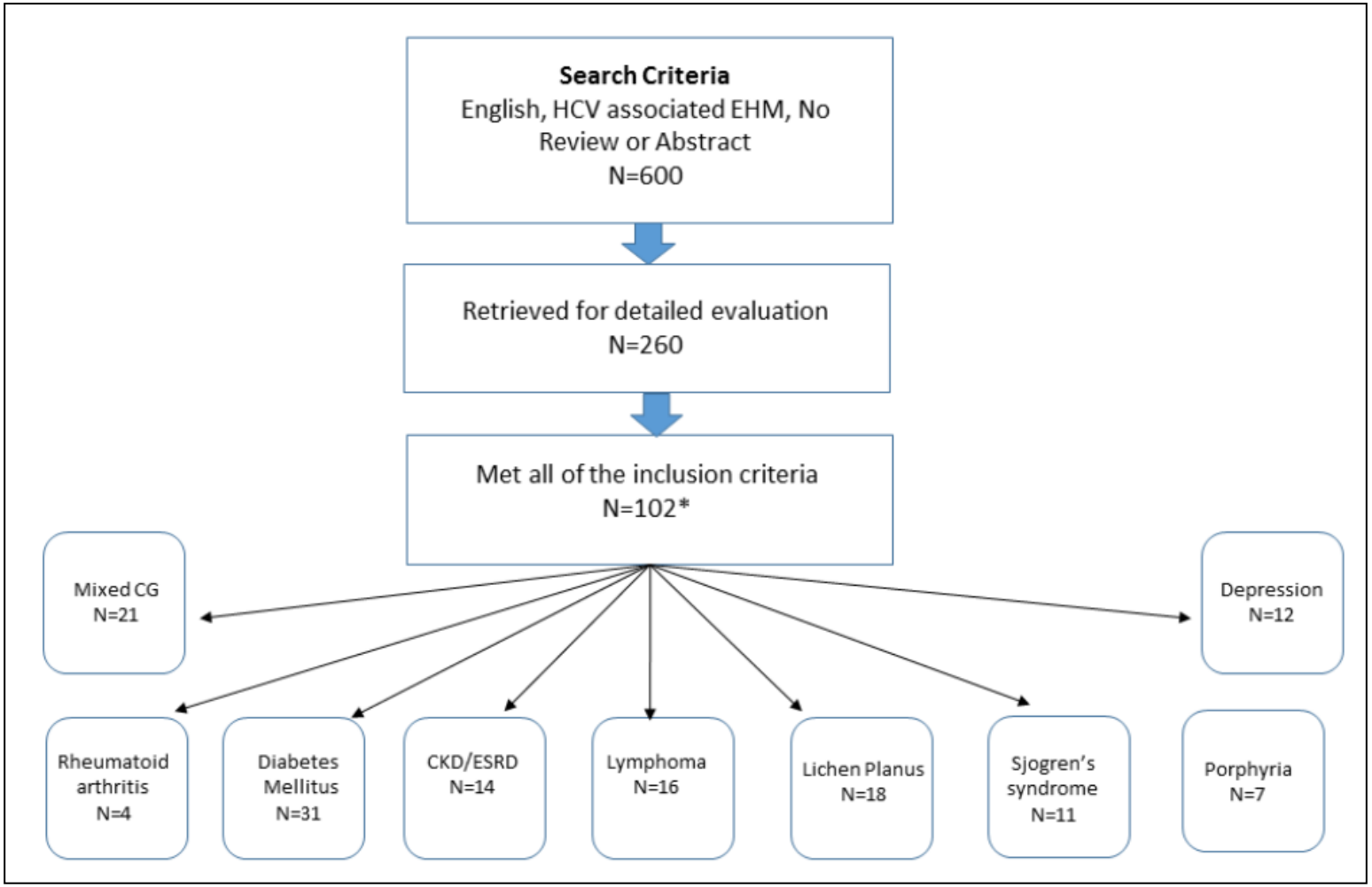
Extrahepatic manifestations of chronic hepatitis C virus infection

Patrice Cacoub[a,b,c,d,*], Laura Gragnani[e], Cloe Comarmond[a,b,c,d], Anna Linda Zignego[e]

Dig Liv Dis 2014

Extra-Hepatic Manifestations of Hepatitis C—a Meta-Analysis of Prevalence, Quality of Life, and Economic Burden

Zobair Younossi[1,2], Haesuk Park[3], Linda Henry[2], Ayoade Adeyemi[3], Maria Stepanova[4]



Gastroenterology 2016, In press

Extra-Hepatic Manifestations of Hepatitis C—a Meta-Analysis of Prevalence, Quality of Life, and Economic Burden

Zobair Younossi[1,2], Haesuk Park[3], Linda Henry[2], Ayoade Adeyemi[3], Maria Stepanova[4]

Table 1. Pooled prevalence and odds ratios for the hepatitis C extrahepatic manifestations: a complete list of Supplementary Table 1.

Extra Hepatic Manifestation	Prevalence in HCV (95% CI)	Prevalence in non-HCV (95% CI)	Odds Ratio (95% CI)*	No. of studies included in HCV and non-HCV (sample size)
Mixed Cryoglobulinemia (MC):				21 studies (n=4,145);
- Any MC	30.1% (21.4%-38.9%)	1.9% (0.4-3.4%)	11.50 (4.56-29.00)	7 studies (n=585)
- Symptomatic MC (vasculitis)	4.9%	0.0%		
Chronic renal disease (including end-stage)	10.1% (6.7%-13.4%)	7.6% (4.7%-10.5%)	Risk ratio: 1.23 (1.12-1.34)	14 studies (n=336,227 HCV; n=2,665,631 non-HCV)
Diabetes mellitus	15% (13%-18%)	10% (6%-15%)	1.58 (1.30-1.86)	31 studies (n=61,843); 19 studies (n=202,130)
Lymphoma	NA	NA	Risk ratio: 1.60 (1.34-1.86)	16 studies **
Lichen Planus	1.9% (1.2%-2.5%)	1.1% (0.3%-1.8%)	2.27 (1.41-5.66)	18 studies (n=40,063); 8 studies (n=138,811)
Sjogren's syndrome	11.9% (7.6%-16.2%)	0.7% (0.00%-3.3%)	2.29 (0.19-27.09)	11 studies (n=38,789); 2 studies (n=136,845)
Porphyria cutanea tarda	0.5% (0.1-0.8)	0.0% (0.0-0.1)	8.53 (4.15-17.52)	7 studies (n=970,315); 3 studies (n=18,763,644)
Rheumatoid arthritis	1.0% (0.0%-2.0%)	0.09% (0.00%-0.09%)	2.39 (1.52-3.77)	4 studies (n=10,970); 1 study (n=199,568)
Depression	24.5% (14.1%-34.9%)	17.2% (13.4%-21.0%)	2.30 (1.31-4.01)	12 studies (n=139,039); 3 studies (n=127,506)

Gastroenterology 2016, In press

Extra-Hepatic Manifestations of Hepatitis C—a Meta-Analysis of Prevalence, Quality of Life, and Economic Burden

Zobair Younossi[1,2], Haesuk Park[3], Linda Henry[2], Ayoade Adeyemi[3], Maria Stepanova[4]

Table 2. Total yearly costs associated with extrahepatic manifestations (EHMs) of HCV*. (References noted in Supplemental References Table 2)

	Prevalence rate of EHMs				Direct medical costs	
Extrahepatic condition	Prevalence in HCV‡	Range for sensitivity analysis†	Baseline prevalence to subtract	Per patient per year [a], $	Total yearly, $mln	Yearly cost, sensitivity analysis, $mln
Symptomatic MC (vasculitis)	4.9%	4.2% to 5.7%	0.0%	$916	$120.26M	$101.85M to $138.67M
Chronic renal disease	16.2% [&]	15.5% to 17.0%	13.2% [32]	$189	$15.39M	$11.71M to $19.07M
ESRD	0.21% [&]	0.20% to 0.22%	0.17% [33]	$71,124	$74.53M	$56.71M to $92.35M
Diabetes mellitus type 2	15.0%	14.0% to 17.0%	9.3% [34]	$2,903	$443.39M	$365.6M to $598.96M
Lymphoma	0.38% [&]	0.35% to 0.41%	0.24% [35]	$6,804	$26.03M	$20.40M to $31.65M
Lichen planus	1.9%	1.6% to 2.2%	1.1%	$127	$2.73M	$1.53M to $3.58M
Sjogren's syndrome	11.9%	9.8% to 14.1%	0.7%	$278	$83.43M	$67.42M to $99.45M
Porphyria cutanea tarda	0.5%	0.3% to 0.6%	0.0%	$2,166	$29.02M	$17.41M to $34.83M
RA-like arthritis	1.0%	0.6% to 1.6%	0.1%	$409	$9.86M	$4.93M to $15.89M
Depression	24.5%	19.3% to 29.7%	17.2%	$2,201	$430.66M	$123.89M to $737.43M
Cardio-vascular disease	12.1% [&]	11.3% to 13.1%	10.3% [9]	$4,066 [36]	$197.47M	$113.99M to $303.23M
Stroke	1.9% [&]	1.7% to 2.3%	1.4% [9]	$5,589 [36]	$72.86M	$36.37M to $133.25M

Gastroenterology 2016, In press

Main extra epatic manifestations of HCV according to the strenght of the association

A. Significant prevalence, consistent pathogenetic data and "ex-adjuvantibus" criteria
- Mixed cryoglobulinaemia/cryoglobulinaemic vasculitis
- B-cell NHL

B. Higher prevalence than controls
- Type 2 diabetes mellitus type 2
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Cardiovascular disorders (i.e. stroke, ischemic heart disease)
- Sicca syndrome
- Arthralgia/myalgia
- Auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)
- Monoclonal gammopathies
- Immune thrombocytopenia
- Porphyria cutanea tarda
- Lichen planus

C. Possible association
- Polyarthritis
- Pruritus
- Fibromyalgia
- Chronic polyradiculoneuropathy
- Lung alveolitis

D. Anecdotal association
- Polymyositis
- Dermatomyositis
- Polyarteritis nodosa
- Psoriasis
- Mooren corneal ulcer
- Erythema nodosum

E. Association with antiviral treatment (interferon alpha)
- Hypo-hyperthyroidism
- Depression
- Fatigue
- Impaired quality of life
- Sarcoidosis
- Lichen
- Skin vasculitis
- Peripheral neuropathy

Cacoub P, DLD 2014

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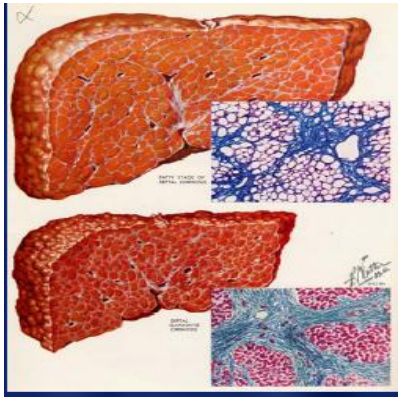
- Peripheral neuropathy

Cacoub P, DLD 2014

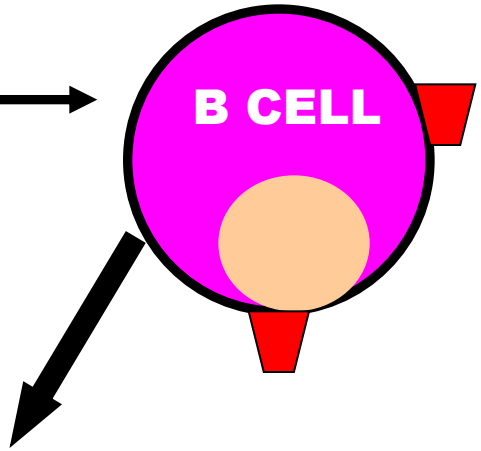
Target dell'infezione cronica da HCV

- Epatotropismo



- **chronic liver disease**
- **cirrosis**
- **HCC**

- Linfotropismo



Manifestazioni extra-epatiche (MEE-HCV)

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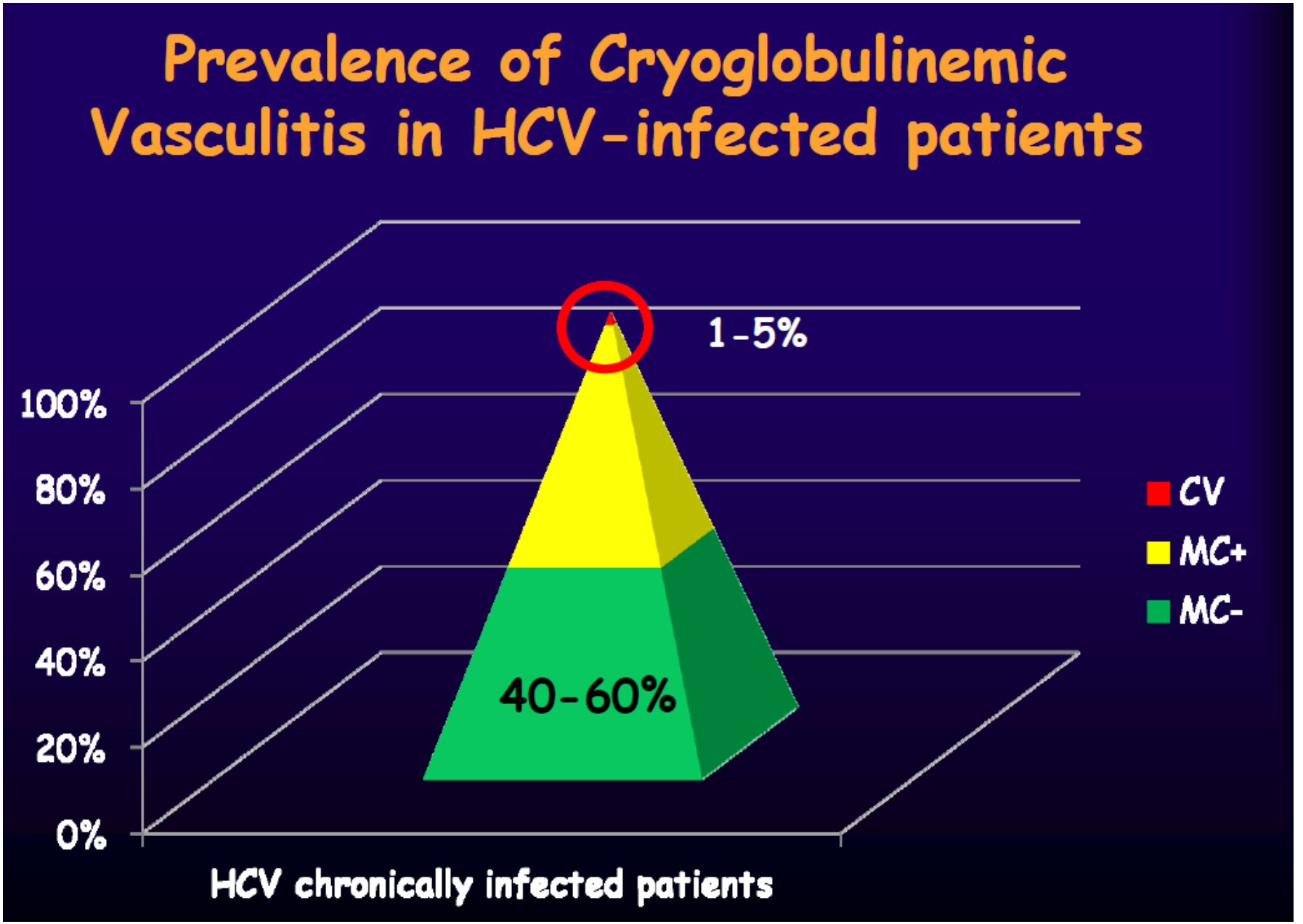
- Peripheral neuropathy

Cacoub P, DLD 2014

Prevalence of Cryoglobulinemic Vasculitis in HCV-infected patients



Prevalence of mixed cryoglobulinaemia syndrome and circulating cryoglobulins in a population-based survey: the Origgio study

Giuseppe Monti [a], Francesco Saccardo [a], Laura Castelnovo [a], Paola Novati [a], Salvatore Sollima [b], Agostino Riva [b], Piercarlo Sarzi-Puttini [c], Luca Quartuccio [d], Salvatore De Vita [d], Massimo Galli [b,*]

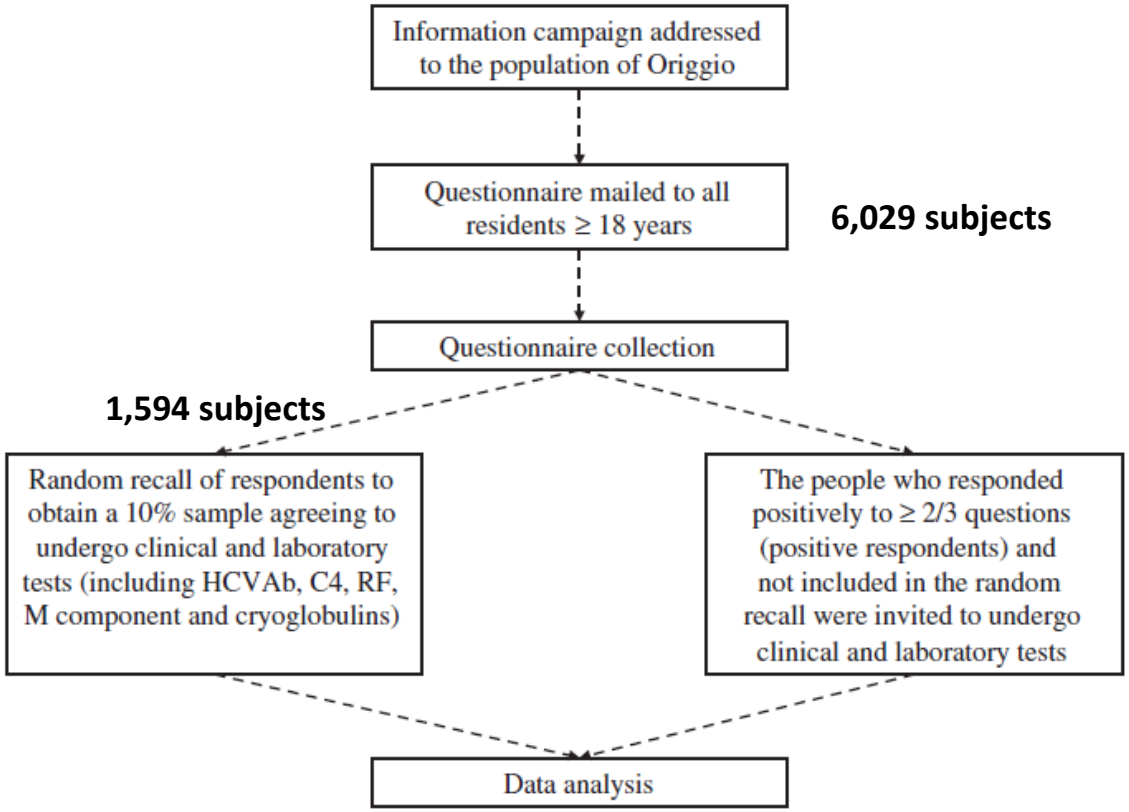
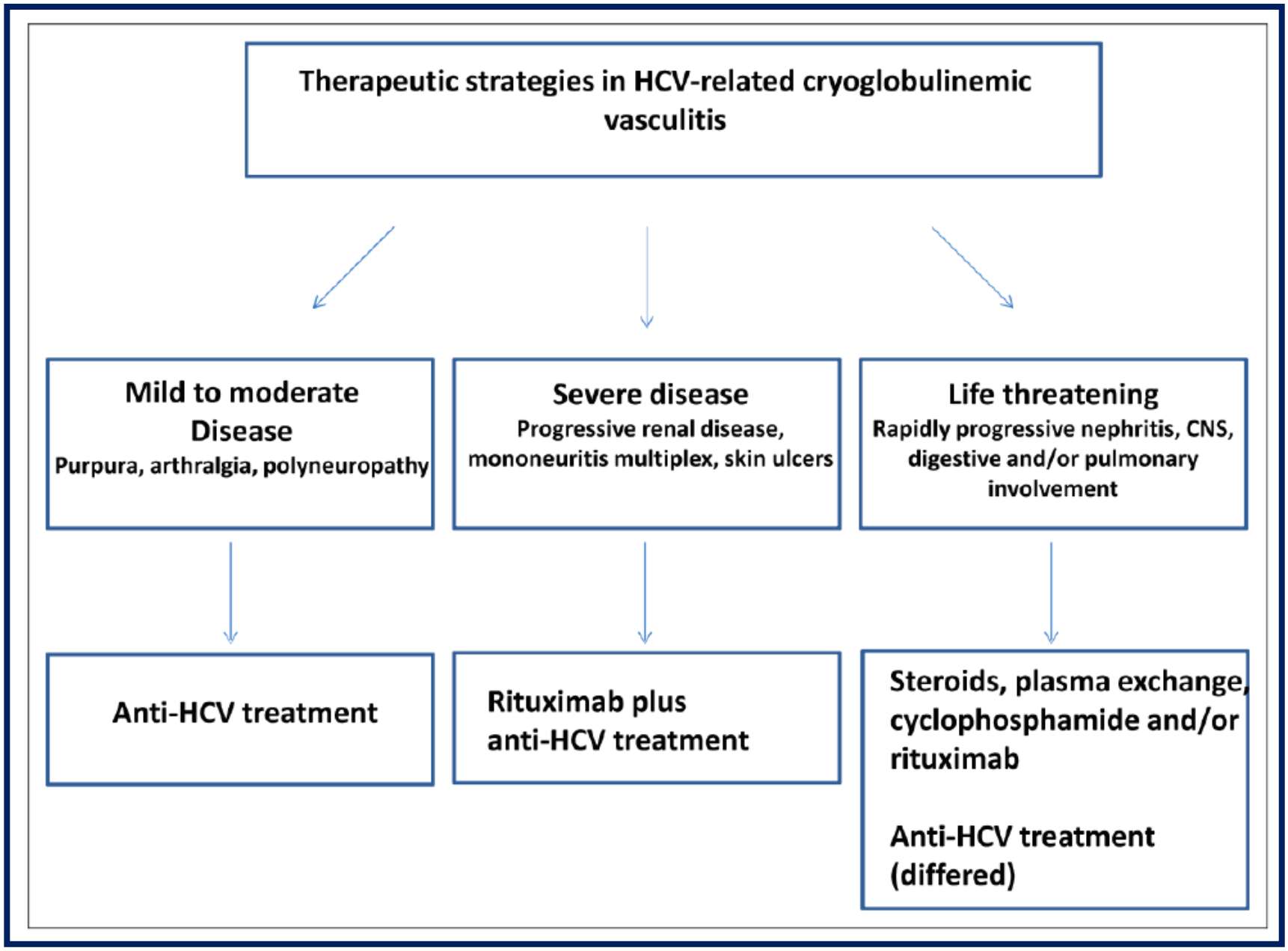


Fig. 1. Study flow chart.

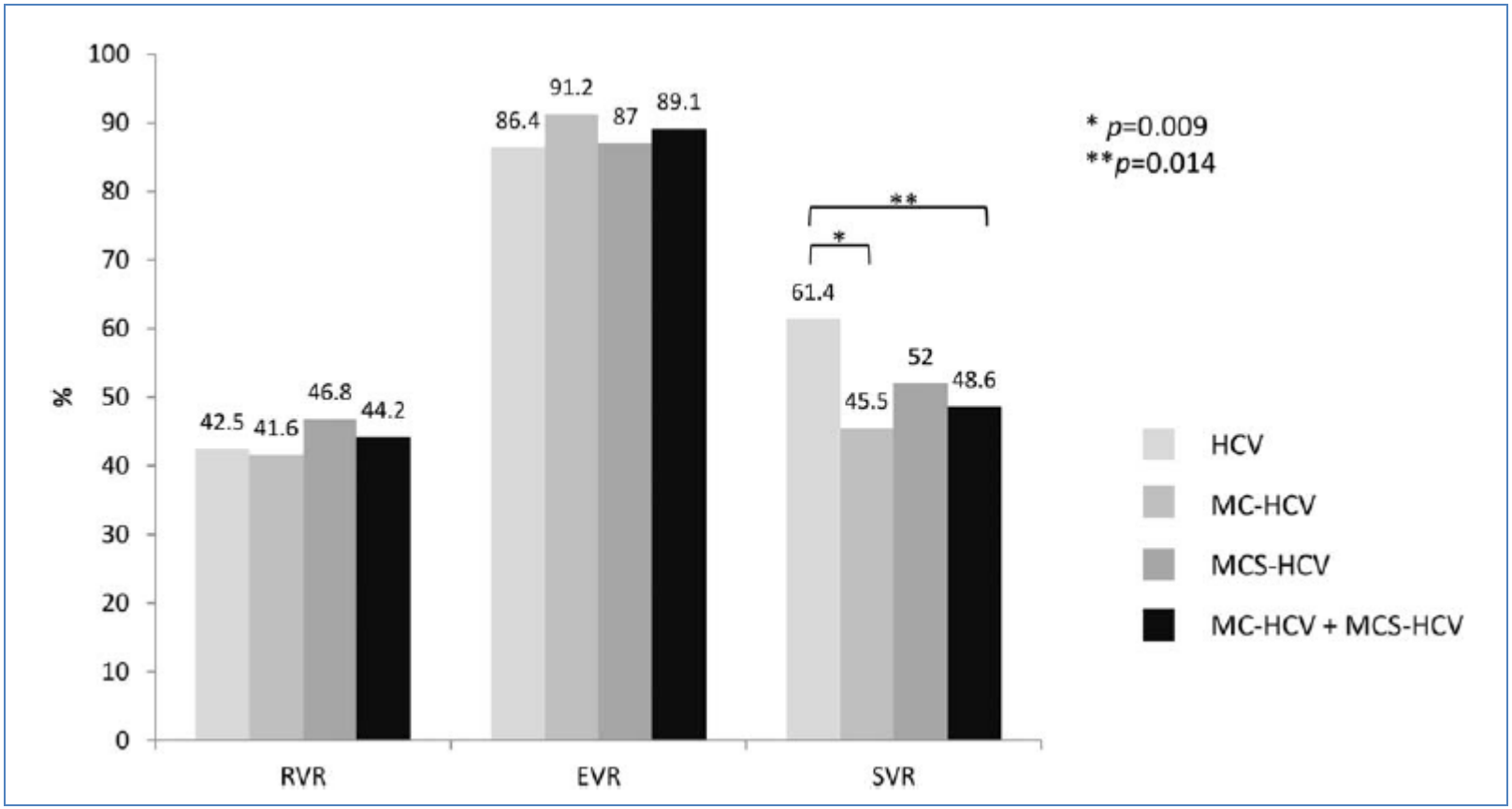
147 subjects accepted → **30 (20.4%): asymptomatic type III cmcgs**
4 (2,7%): MCS



Rosenthal E, Lupus 2015

Long-Term Effect of HCV Eradication in Patients With Mixed Cryoglobulinemia: A Prospective, Controlled, Open-Label, Cohort Study

424 HCV patients treated with Peg-IFN plus ribavirin with a follow-up post-treatment of 35 -124 months (mean 92.5 months):
- **121 patients with symptomatic MC (MCS-HCV);**
- **132 patients with asymptomatic MC (MC-HCV);**
- **58 patients without MC (HCV)**



Gragnani L, Hepatology 2015

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correlated with the virological one. All patients with sustained virological response also experienced a sustained clinical response, either complete or partial. In the majority of sustained virological response patients all MCS symptoms persistently disappeared (36 patients, 57%); in only two (3%) did definite MCS persist. All virological nonresponders were also clinical nonresponders, in spite of a transient improvement in some cases. No evolution to lymphoma was observed. For the first time we have evaluated both the effects

Patients with MCS were characterized by more frequent adverse events than controls. In fact, at least one adverse event was observed in 35 (28.9%) MCS-HCV patients and in 17 (10.7%) HCV patients ($P = 0.009$).

Gragnani L, Hepatology 2015

Treatment of Hepatitis C Virus–Associated Mixed Cryoglobulinemia with Direct-Acting Antiviral Agents

Table 1. Baseline Demographics and Clinical Characteristic of Patients With HCV-MCS Treated With Sofosbuvir-Based DAA Therapy (n = 12)

Parameter	Median (Range) or Count (
Age, years	61 (37-73)
Male (%)	7 (58%)
Race (%)	
Caucasian	6 (50%)
African American	2 (17%)
Hispanic	4 (33%)
Cirrhosis	6 (50%)
Hepatocellular carcinoma (prior)	1 (8%)
Diabetes (%)	0%
Hypertensive (%)	10 (83%)
Number of antihypertensive medications	2 (0-5)
BMI (kg/m^2)	28.3 (22.7-34.1)
Duration of HCV infection (years)	30 (10-53)
Genotype	
1a	5 (42%)
1b	2 (17%)
1 untypable	1 (8%)
2b	2 (17%)
3	1 (8%)
4	1 (8%)
Prior treatment experience	
Previously treated	6 (50%)
Treatment-naive	6 (50%)
Treatment regimen prescribed	
SOF/SIM 12 weeks	8 (67%)
SOF/RBV 12 weeks	2 (17%)
SOF/RBV 24 weeks	2 (17%)
Duration of known cryoglobulinemia (years)	5 (0.5-21)
Baseline clinical presentation*	
Glomerulonephritis	7 (58%)
Purpura	6 (50%)
Arthralgia	6 (50%)
Peripheral neuropathy	4 (33%)
Raynaud's phenomenon	2 (17%)
Sicca	1 (8%)
Renal arteritis/infarct	1 (8%)

SVR_{12}: 83%
Serious ADR: 17%

Sise ME, Hepatology,2015

Treatment of Hepatitis C Virus–Associated Mixed Cryoglobulinemia with Direct-Acting Antiviral Agents

Table 3. Clinical Symptoms, Serology, and Immunosuppression Required Before and After DAA Therapy

		Pretreatment					Posttreatment		
Patient	Duration Cryo (Years)	Symptoms	Serology	On-Treatment Immunosuppression	Regimen	SVR	Persistent Symptoms	Serology	Immunosuppression
1	5	NHBCL, neuropathy, Raynaud's, arthralgia, GN	Cryo 4% C3 57 C4 2 RF-positive	Rituximab	SOF/SIM	Yes	Neuropathy GN	Cryo 3% C3 148 C4 6 RF-positive	None
2	21	Neuropathy, Sicca, Raynaud's, purpura, GN	Cryo 2% C3 72 C4 16 RF-positive	None	SOF/SIM	Yes	Reynaud's, GN	Cryo-negative C3 ND C4 ND RF ND	None
3	1	Purpura, skin ulcers, arthralgias, GN	Cryo 1% C3 99 C4 6 RF-positive	None	SOF/RIBA	Yes	Arthralgia	Cryo trace C3 90 C4 18 RF-positive	None
4	10	GN	Cryo 3% C3 82 C4 13 RF-positive	None	SOF/SIM	Yes	GN	Cryo 1% C3 115 C4 16 RF ND	None
5	5	Neuropathy, purpura, GN	Cryo 0.5% C3 111 C4 29 RF ND	None	SOF/SIM	Yes	None	Cryo-negative C3 ND C4 ND RF ND	None
6	3	GN	Cryo 2% C3 ND C4 ND RF-positive	None	SOF/SIM	Yes	None	Cryo ND C3 ND C4 ND RF ND	None
7	7	Arthralgia, GN	Cryo 1% C3 51 C4 11 RF-negative	Ustekinumab (psoriasis)	SOF/SIM	No	Arthralgia, GN	Cryo-negative C3 85 C4 15 RF-negative	Ustekinumab (psoriasis)
8	5	Purpura, arthralgia	Cryo 2% C3 79 C4 2 RF-positive	None	SOF/SIM	Yes	None	Cryo ND C3 ND C4 ND RF ND	None
9	0.5	Neuropathy, purpura	Cryo 0.5% C3 66 C4 5 RF-positive	Rituximab	SOF/RIBA	Yes	Neuropathy	Cryo ND C3 ND C4 ND RF ND	Rituximab
10	6	Purpura, arthralgia, renal artery vasculitis	Cryo 1% C3 89 C4 12 RF-positive	Rituximab	SOF/RIBA	No	Purpura, arthralgia, renal artery vasculitis	Cryo 2% C3 103 C4 6 RF-negative	Rituximab and prednisone
11	1	Arthritis	Cryo 3% C3 89 C4 27 RF-positive	Rituximab	SOF/RIBA	Yes	Arthritis	Cryo 1% C3 110 C4 30 RF-positive	Rituximab
12	1	Arthritis	Cryo 1% C3 65 C4 9 RF-positive	None	SOF/SIM	Yes	None	Cryo- negative C3 124 C4 21 RF ND	None

Sise ME, Hepatology,2015

Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study

Objective To evaluate safety and efficacy of an oral interferon-free regimen, sofosbuvir plus ribavirin, in HCV-cryoglobulinaemia vasculitis.

Table 1 Baseline characteristics of the 24 patients with HCV-cryoglobulinaemia vasculitis

	N=24
Age, years	56.5 (49.5–66.5)
Female gender (n, %)	11 (46)
HCV infection characteristics	
HCV genotype (n, %)	
1a	6 (25)
1b	6 (25)
2	2 (8)
3	6 (25)
4	3 (13)
5	1 (4)
Metavir liver fibrosis score (n, %)	
Stage 1	5 (21)
Stage 2	5 (21)
Stage 3	2 (8)
Stage 4	12 (50)
Median baseline HCV RNA (log_{10} IU/mL)	5.9 (4.5; 6.3)
Median ALT level (IU/L)	48.5 (28; 68)
Haematological variables	
Median haemoglobin count (g/dL)	13.3 (12; 15)
Median neutrophil count ($10^3/mm^3$)	2.9 (2.3; 4)
Median platelet count ($10^3/mm^3$)	175 (115; 264)
Previous virological response to antiviral therapy	
Naive	11 (46)
No response	9 (37)
Relapse*	4 (17)
Mixed cryoglobulinaemia-related	
Median serum cryoglobulin level (g/L)	0.36 (0.2; 0.8)
Median serum C4 level (g/L)	0.10 (0.07; 0.19)
Median serum rheumatoid factor level (IU/mL)	26 (6; 84)
Vasculitis (n, %)	
Purpura	16 (67)
Skin ulcer	3 (13)
Skin necrosis	1 (4)
Arthralgia	14 (58)
Polyneuropathy	16 (67)
Kidney involvement	5 (21)

Saadoun D, Ann Rheum Dis 2016

Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study

Table 2 Responses during and after treatment

	Clinical response		Virological response HCV RNA <12 IU/mL
	CR	PR	
At baseline	–	–	–
During treatment, n=24			
At week 4	6	1	1
At week 8	4	–	19
At week 12	7	2	2
At week 16	3	–	–
At week 20	1	–	–
At week 24	21/24 (87.5)	3/24 (12.5)	22/24 (91.7)
After the end of treatment			
At week 12	20/23 (86.9)*		17/23 (74)†

Saadoun D, Ann Rheum Dis 2016

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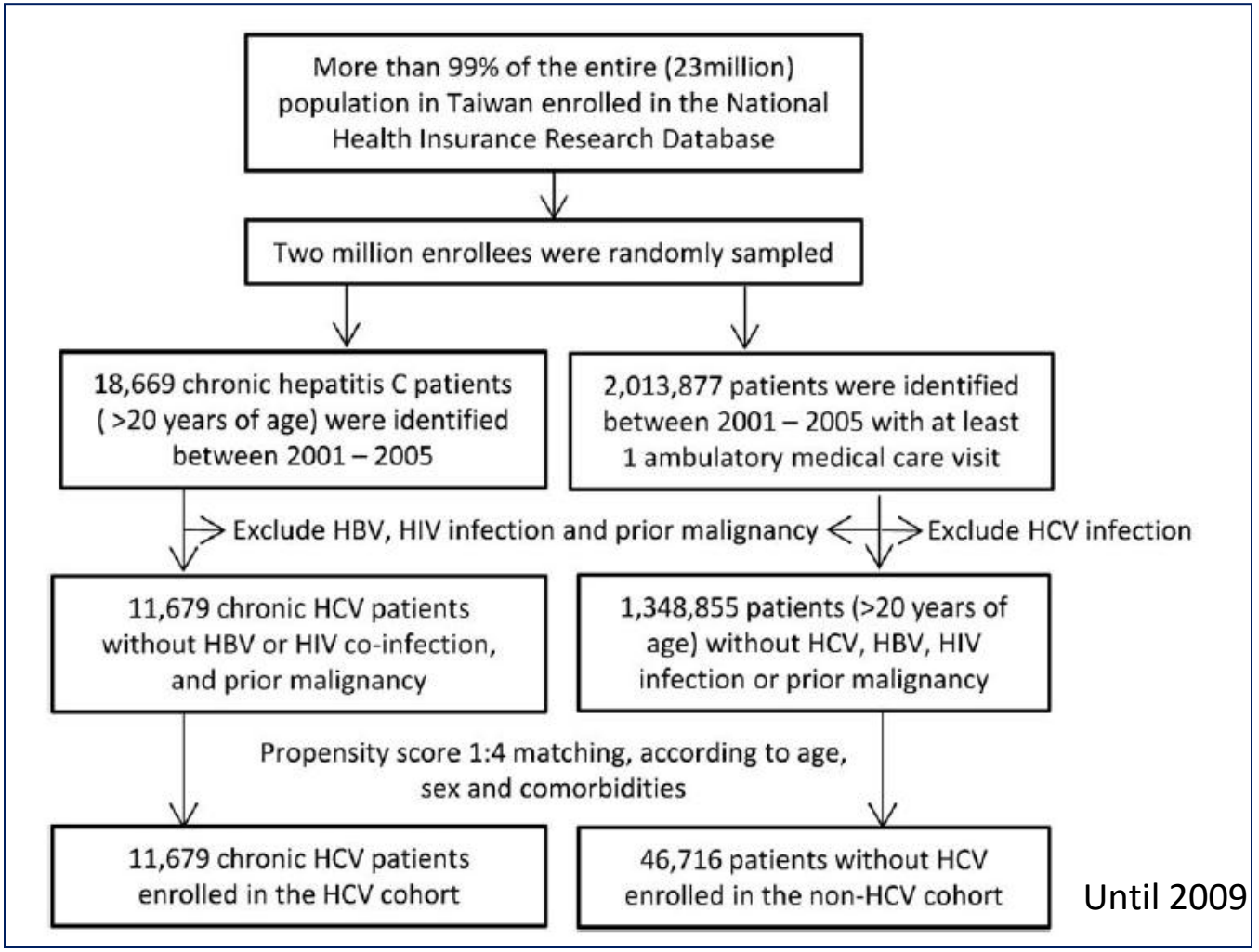
- Depression
- Fatigue
- Impaired quality of life
- Sarcoidosis
- Lichen
- Skin vasculitis
- Peripheral neuropathy

Cacoub P, DLD 2014

Hepatitis C Viral Infection Increases the Risk of Lymphoid-Neoplasms: A Population-Based Cohort Study



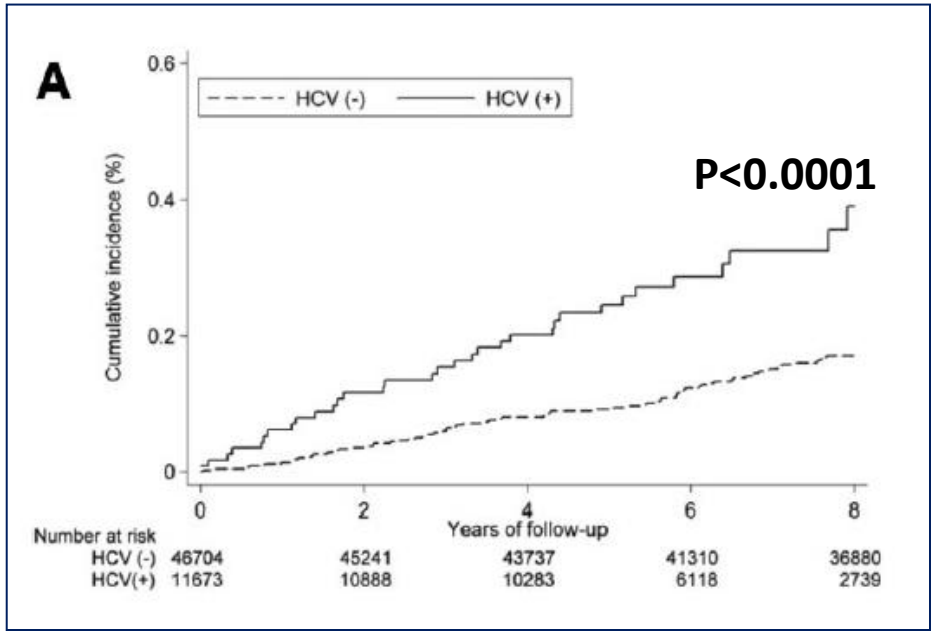
Until 2009

Su ,TH Hepatology 2016

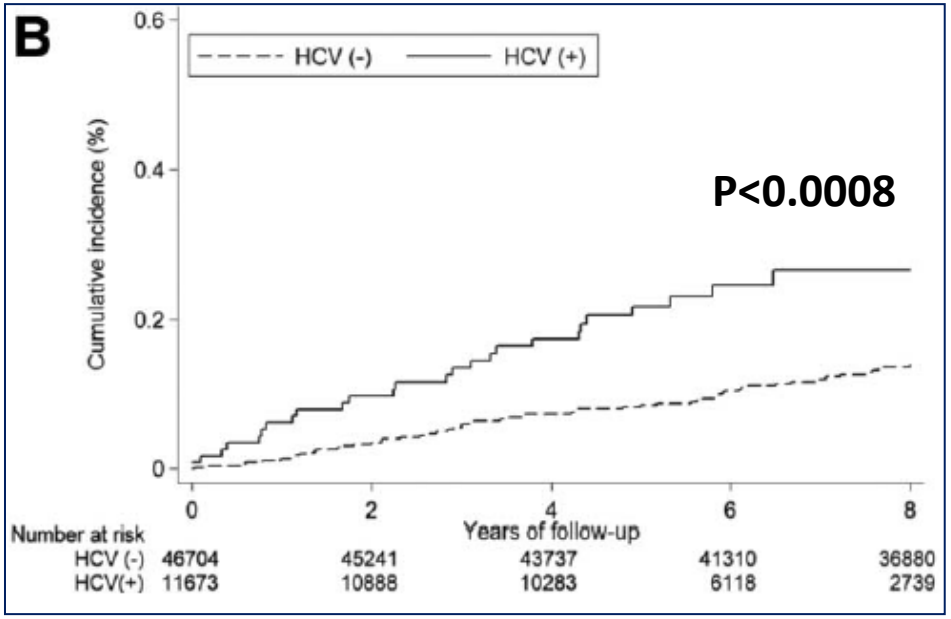
Hepatitis C Viral Infection Increases the Risk of Lymphoid-Neoplasms: A Population-Based Cohort Study

Cumulative incidence of lymphoma by the HCV and non-HCV cohorts

any lymphoid-neoplasm



non-Hodgkin lymphoma

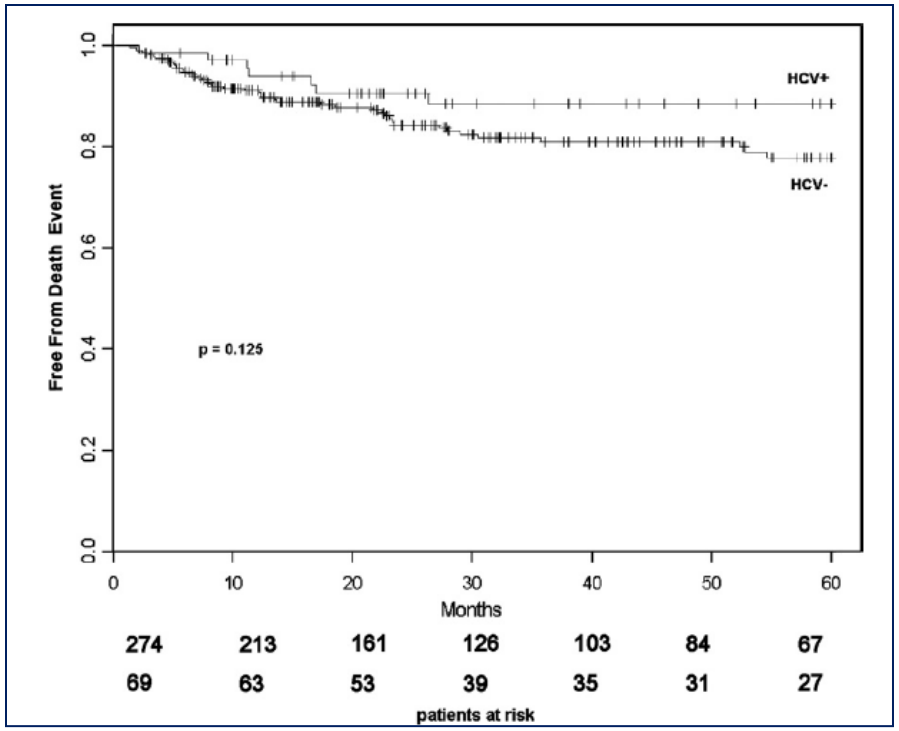


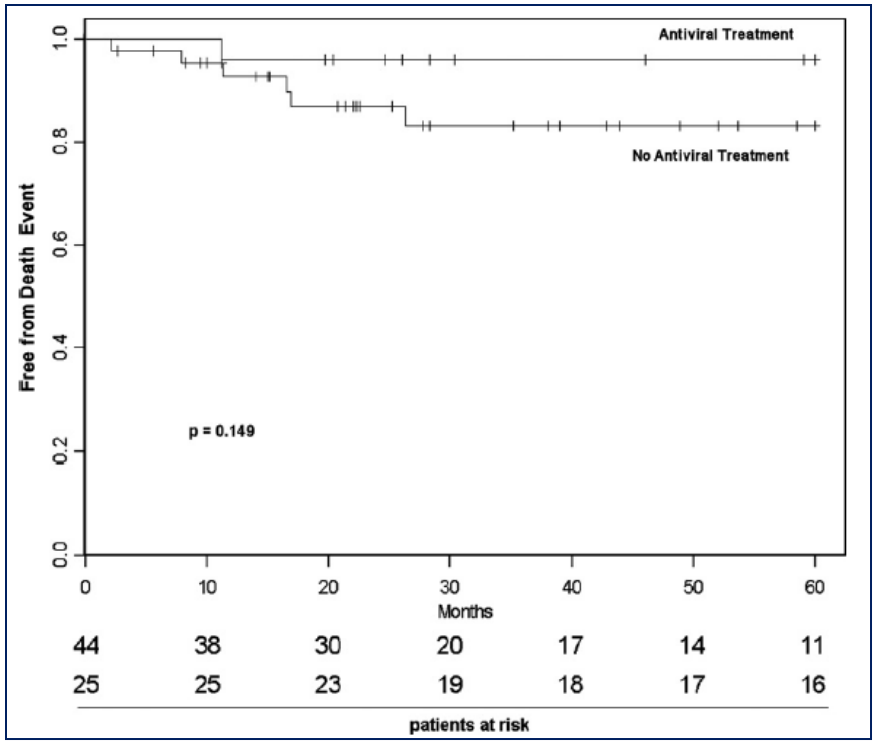
Su ,TH Hepatology 2016

Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma☆

343 chemotherapy-treated patients with NHL were retrospectively evaluated:
-69 HCV positive (25 treated with antiviral therapy; 44 without)
-274 HCV negative

Overall survival





La Mura V, J Hepatol 2008

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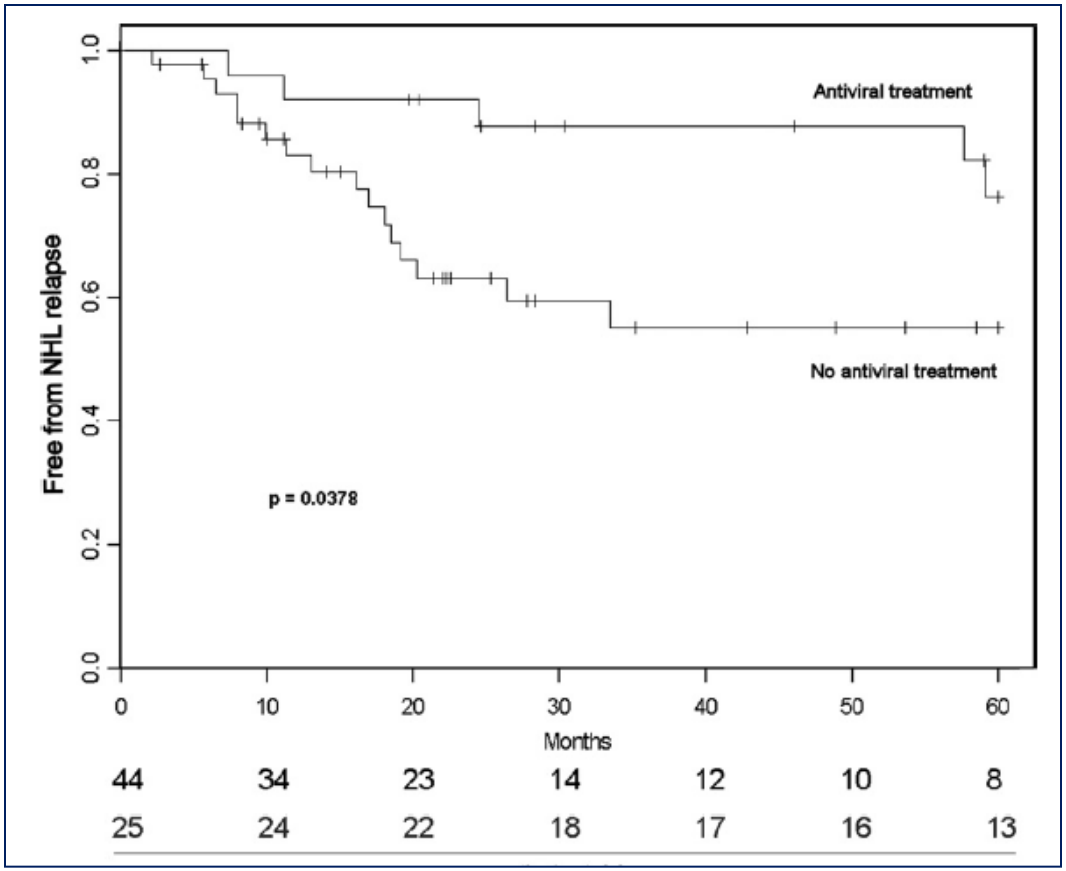
-69 HCV positive (25 treated with antiviral therapy; 44 without)
-274 HCV negative

Desease-free survival in HCV patients according antiviral treatment



La Mura V, J Hepatol 2008

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A. Significant prevalence, consistent pathogenetic data and "ex-adjuvantibus" criteria

- Mixed cryoglobulinaemia/cryoglobulinaemic vasculitis
- B-cell NHL

B. Higher prevalence than controls

- Type 2 diabetes mellitus type 2
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Cardiovascular disorders (i.e. stroke, ischemic heart disease)
- Sicca syndrome
- Arthralgia/myalgia
- Auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)
- Monoclonal gammopathies
- Immune thrombocytopenia
- Porphyria cutanea tarda
- Lichen planus

C. Possible association

- Polyarthritis
- Pruritus
- Fibromyalgia
- Chronic polyradiculoneuropathy
- Lung alveolitis

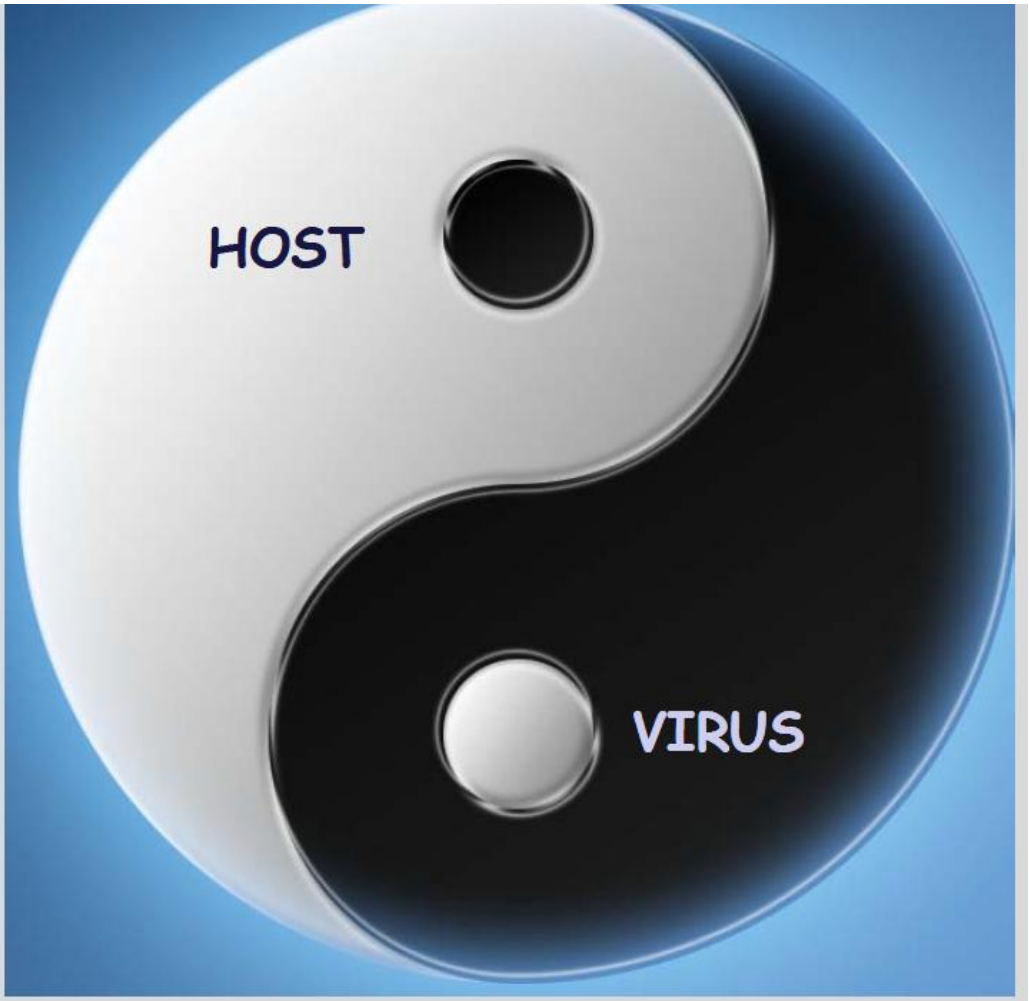
D. Anecdotal association

- Polymyositis
- Dermatomyositis
- Polyarteritis nodosa
- Psoriasis
- Mooren corneal ulcer
- Erythema nodosum

E. Association with antiviral treatment (interferon alpha)

- Hypo-hyperthyroidism
- Depression
- Fatigue
- Impaired quality of life
- Sarcoidosis
- Lichen
- Skin vasculitis
- Peripheral neuropathy

Cacoub P, DLD 2014


HOST
VIRUS

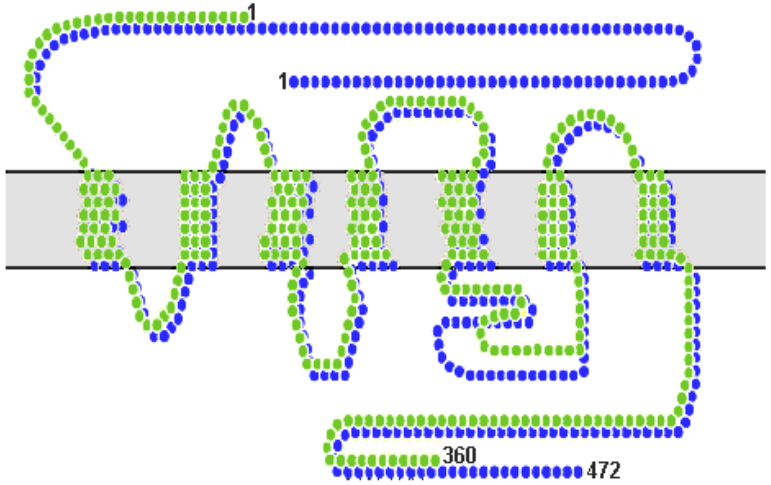
CB2-63 POLYMORPHISM AND IMMUNE-MEDIATED DISEASES ASSOCIATED WITH HCV CHRONIC INFECTION

Nicola Coppola*[1], Rosa Zampino*[2], Giulia Bellini[3], Maria Stanzione[4], Nicolina Capoluongo[1], Aldo Marrone[2], Margherita Macera[1], Luigi Elio Adinolfi[2], Emanuele Miraglia Del Giudice[5], Ivan Gentile[6], Evangelista Sagnelli[1], Francesca Rossi[5]

CROI 2016

Cannabinoid receptors (CB1 and CB2)

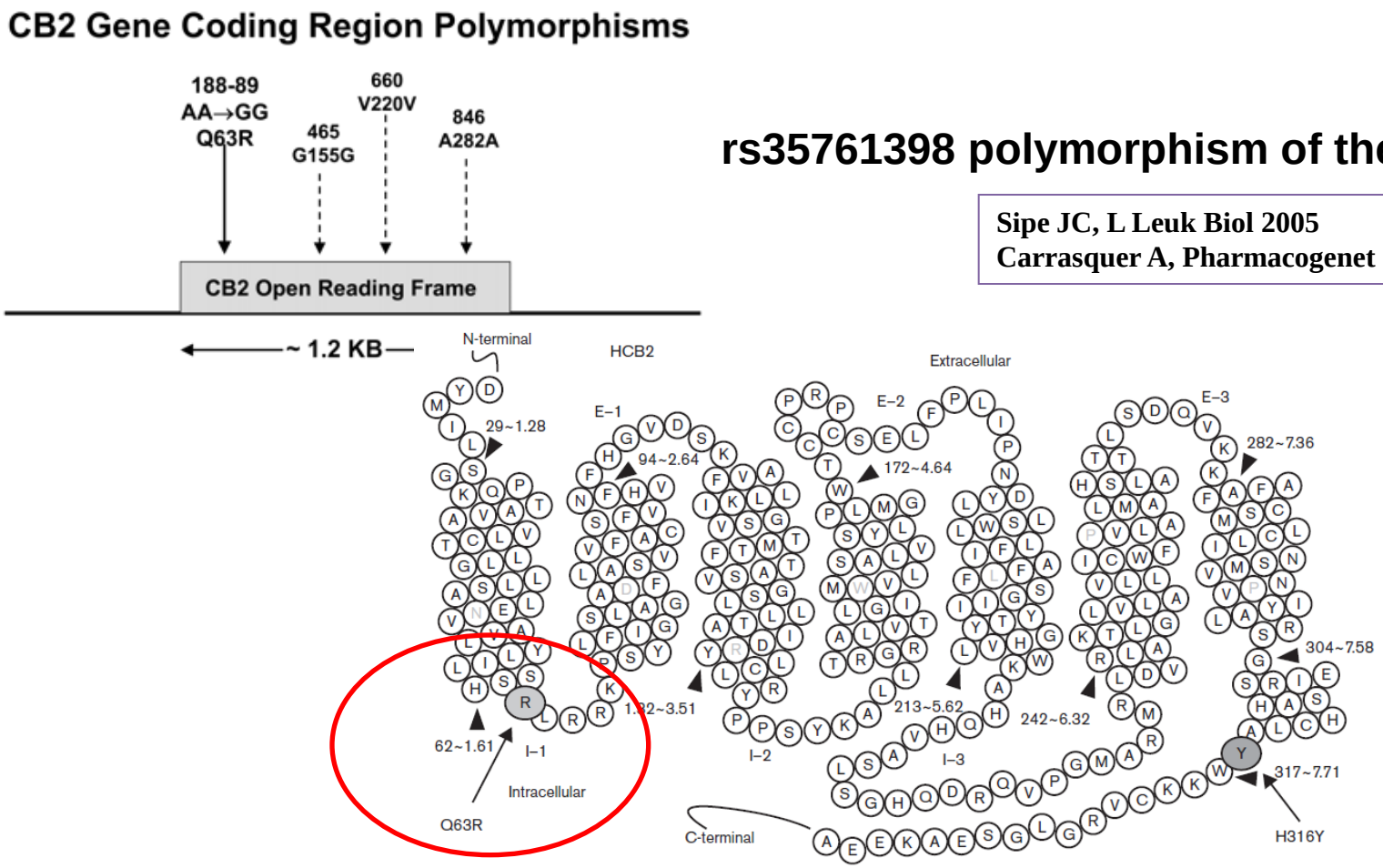
CB1 • CB2 •



CB1 is found in high concentrations in the brain, but is also present in many peripheral tissues such as the liver, adipose tissue and gut.

CB2 is found primarily in the immune system and plays a key role in the modulation of innate immunity
It is also present in peripheral tissues including the liver

Straiker A, J Neurphysiol, 2003; Howlett AC, Pharmacol Rev, 2002; Howlett AC, Handb Exp Pharmacol, 2005; Kunos G, J Biol Chem 2008



rs35761398 polymorphism of the *CNR2* gene

Sipe JC, L Leuk Biol 2005
Carrasquer A, Pharmacogenet Genomics 2010

CB2 carrying arginine (R) at codon 63 had a reduced function when activated by an endogenous cannabinoid

rs35761398 polymorphism	Receptor function
CB2-63 QQ	+
CB2-63 QR	-
CB2-63 RR	--

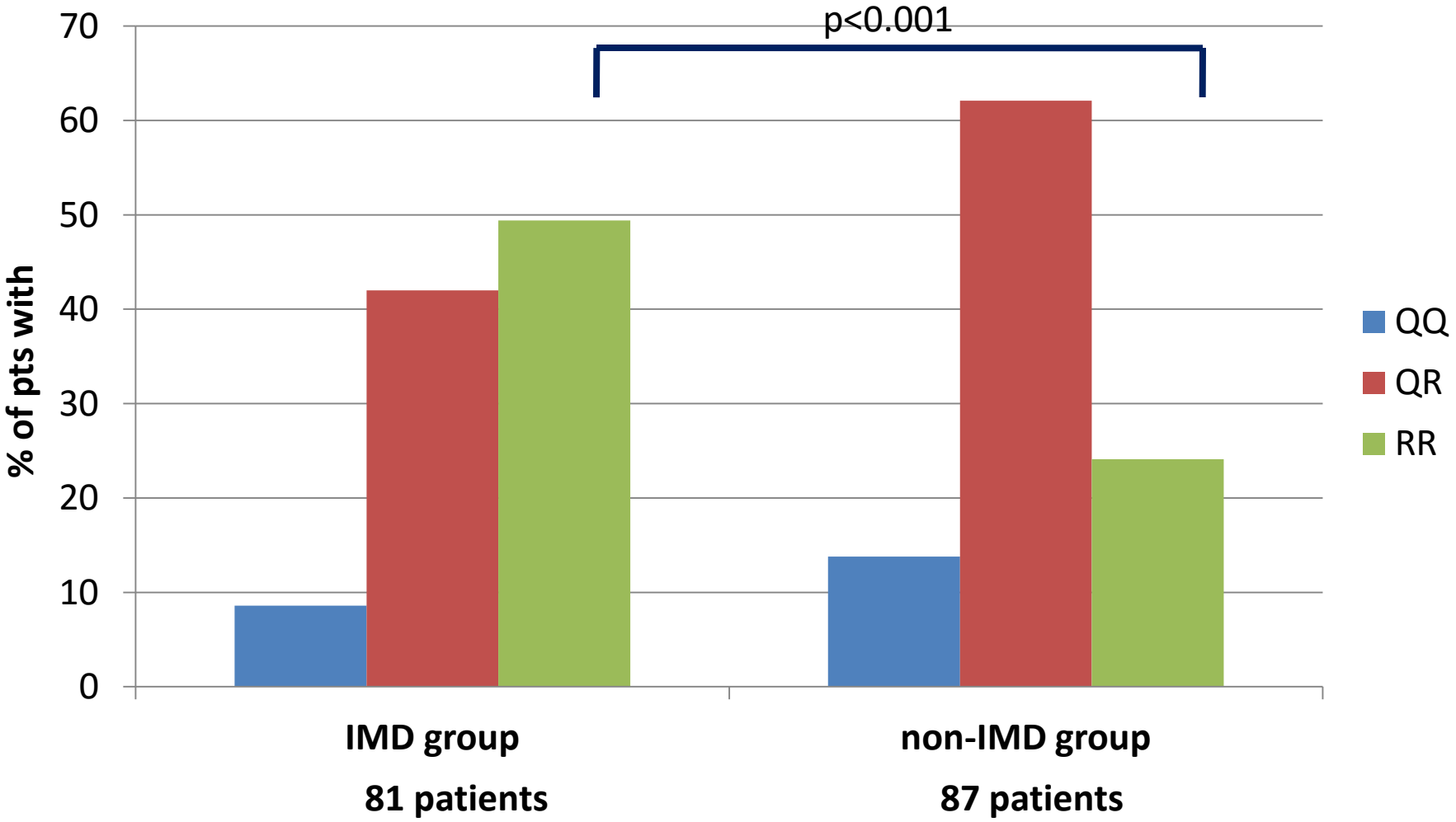
Aims: to evaluate whether CB2 variants are associated with the presence of IMDs in patients with chronic HCV infection.

168 consecutive Caucasian patients with CHC

- 81 with signs of immuno-mediated diseases (IMDs), observed in 12 months
  - ANA positivity (≥1:160) with a homogenous pattern: 22 patients
  - ASMA positivity (≥1:160): 3 patients
  - cryocrit >2% (or >1% with clinical cryoglobulinemia): 24 pts
  - autoimmune thyroiditis: 25 patients
  - B-cell non-Hodgkin lymphoma: 2 patients
  - autoimmune hemolytic anemia: 1 patient
  - psoriasis: 4 patients
- 87 without sign of IMD, observed in 3 months

Coppola N, CROI 2016

CB2-63 variants according to the rpesence or absence of immune-mediated diseases



Coppola N, CROI 2016

CB2-63 variants according to the rpesence or absence of immune-mediated diseases

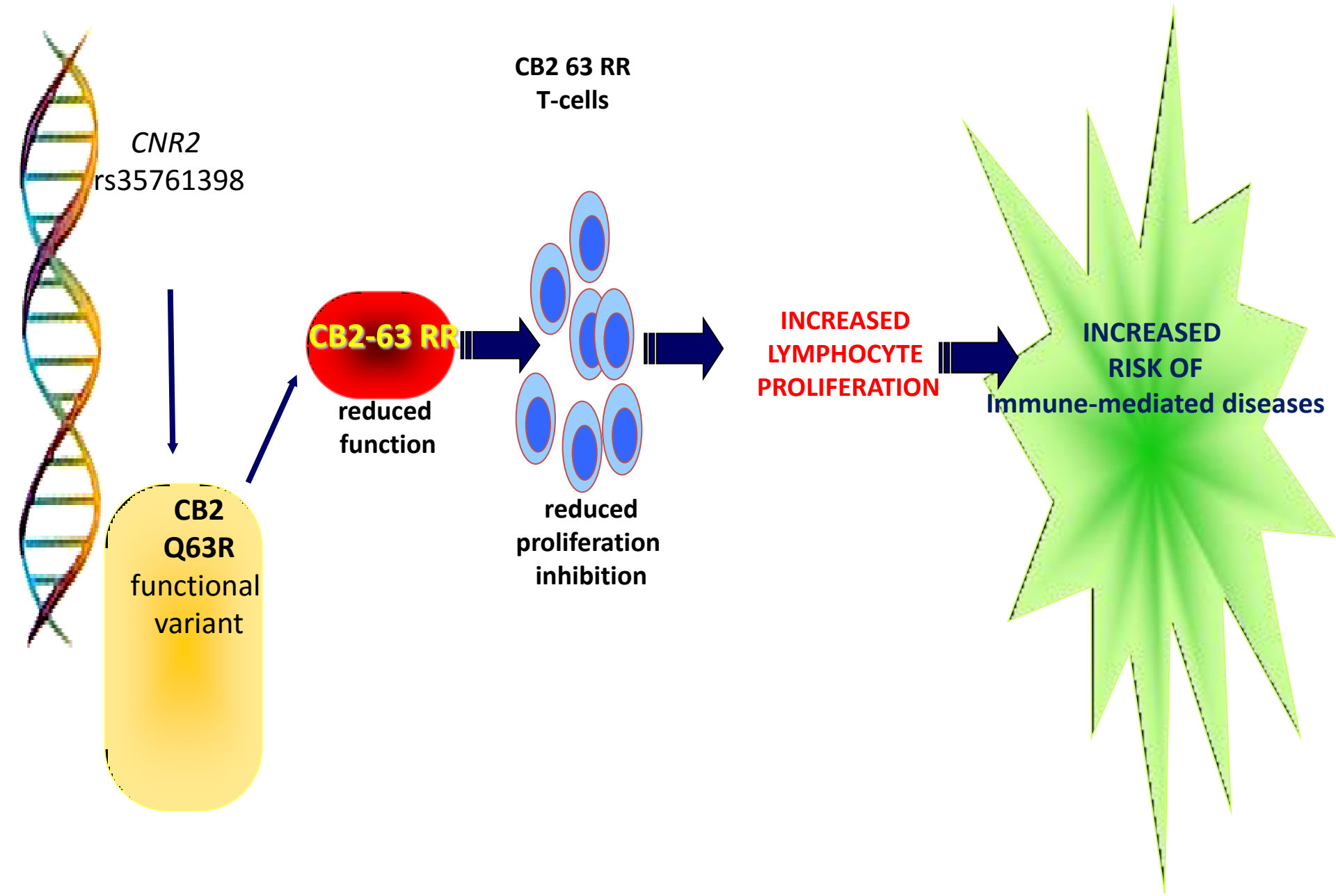
Table 3: Logistic regression between CB2-63 variants and immune-mediated disorders.

Analysis of Variance for immune-mediated diseases					
	Sum of squares	*df*	*Mean of squares*	*F ratio*	*P-value*
Model	3.82338	4	0.955845	4.23	0.0029
Residual	31.8479	141	0.225871		
Total (Corr.)	35.6712	145			

Single factor contribution

	Sum of squares	*df*	*Mean of squares*	*F ratio*	*P value*
CB2	2.41254	2	1.20627	5.34	**0.0058**
Sex	0.416739	1	0.416739	1.85	0.1765
Age	0.672086	1	0.672086	2.98	0.0867
Residual	31.8479	141	0.225871		
Total (corrected)	35.6712	145			

Coppola N, CROI 2016


CB2 63 RR
T-cells
CNR2
rs35761398
CB2-63 RR
reduced
function
CB2
Q63R
functional
variant
reduced
proliferation
inhibition
INCREASED
LYMPHOCYTE
PROLIFERATION
INCREASED
RISK OF
Immune-mediated diseases

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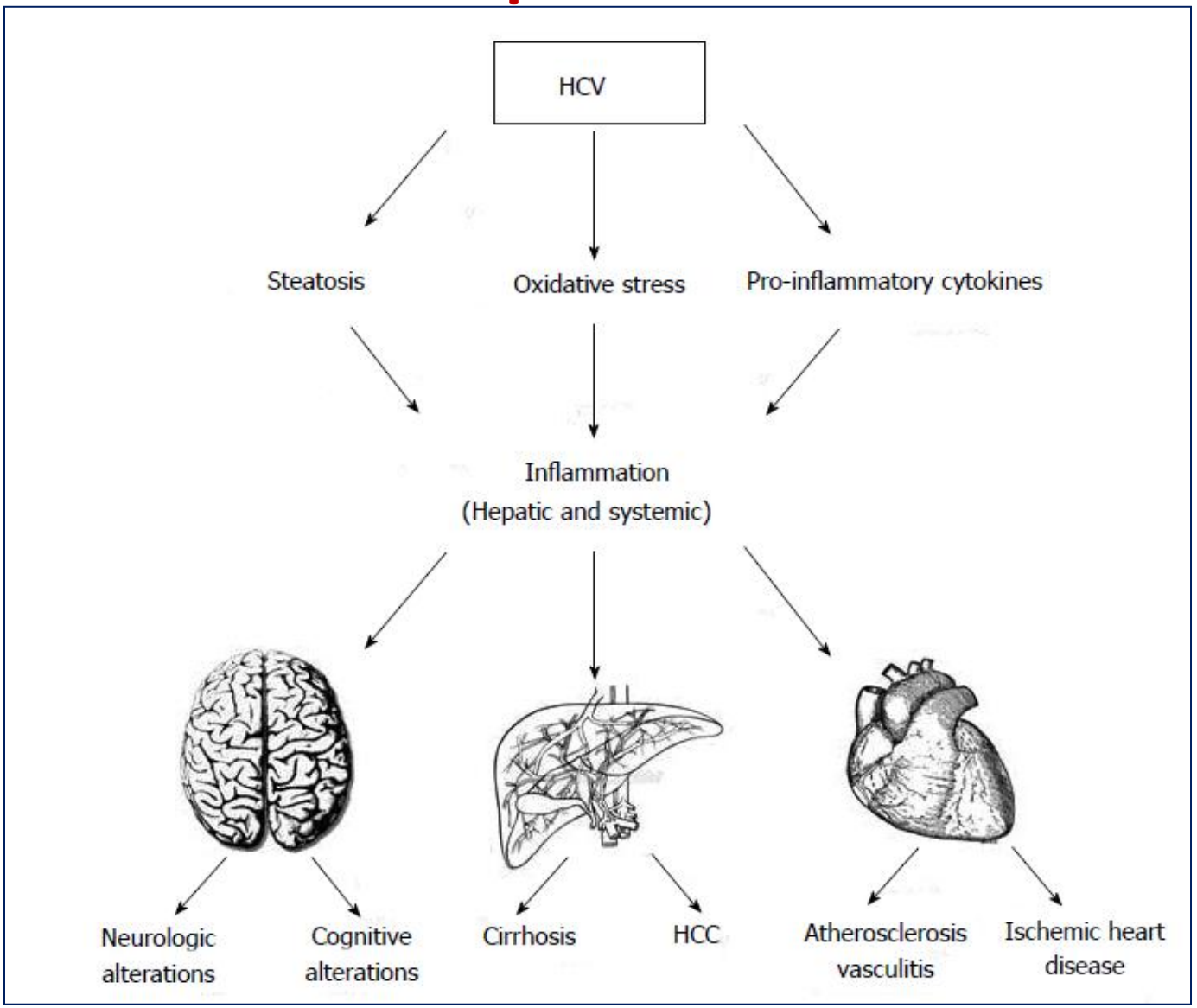
- Sarcoidosis
- Lichen
- Skin vasculitis
- Peripheral neuropathy

Cacoub P, DLD 2014

HCV, chronic inflamation and extra-hepatic conditions



Zampino R, WJG 2013

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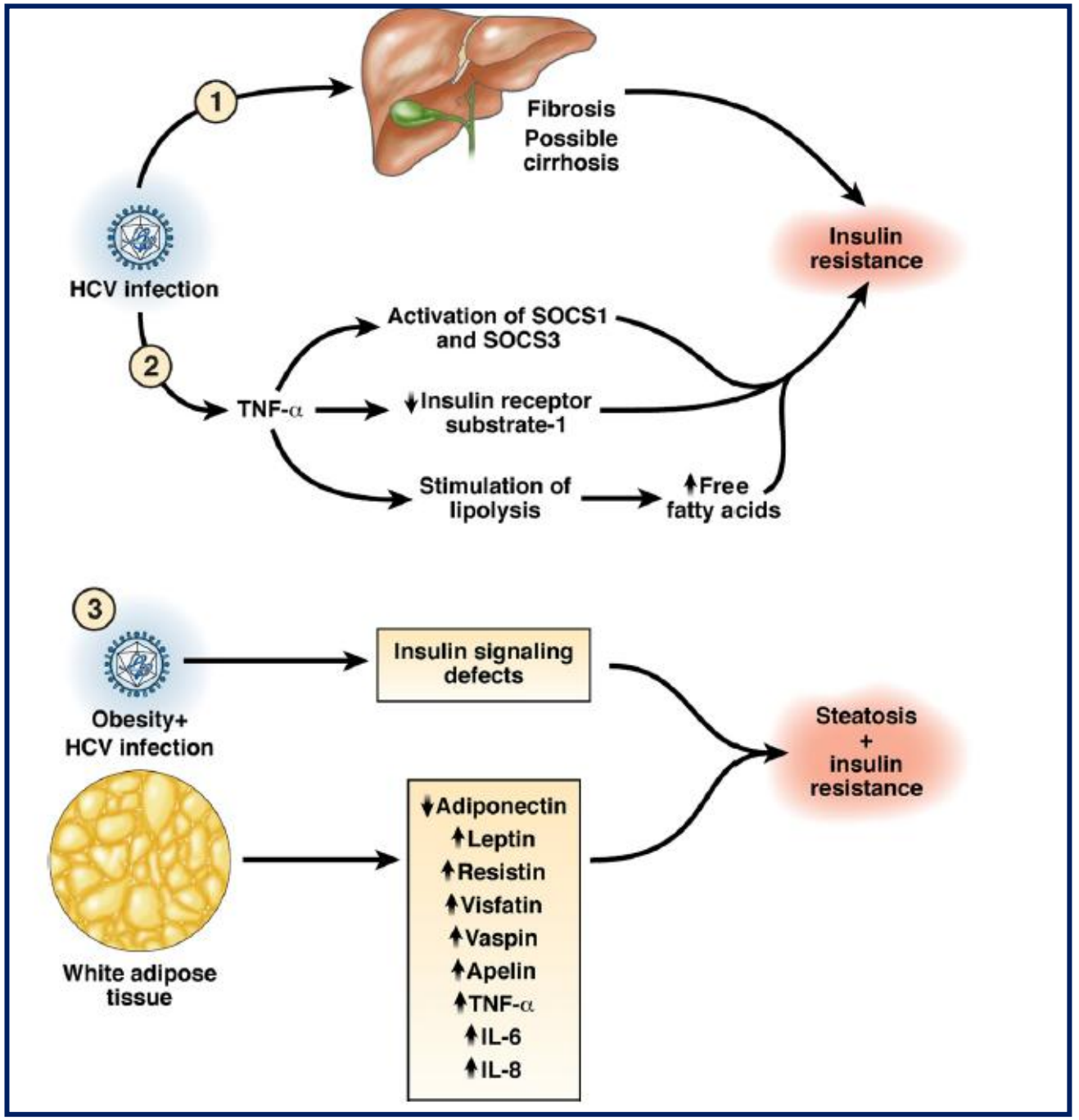
Cacoub P, DLD 2014



Jacobson IM, Clin Gastroenterol Hep 2010

HCV and metabolic effects

Potential effect	Studies and main findings
Diabetes mellitus	Mehta et al, 2000: Based on NHANES data collected between 1988 and 1994, among patients 40 years of age and older, HCV infection was associated with diabetes (OR, 3.77; 95% CI, 1.80–7.87) Wang et al, 2007: Compared with uninfected people, HCV-infected patients had a higher cumulative incidence of diabetes (HR, 1.7; 95% CI, 1.3–2.1) in a community-based longitudinal study Mehta et al, 2003: Among patients at high risk for diabetes, HCV infection increased the risk of diabetes more than 11-fold during 9 years of follow-up (HR, 11.58; 95% CI, 1.39–96.6) Younossi et al, 2013: Based on NHANES data collected between 1999 and 2010, chronic HCV infection was independently associated with diabetes (OR, 2.31; 95% CI, 1.18–4.54), insulin resistance (OR, 2.06; 95% CI, 1.19–3.57), and hypertension (OR, 2.06; 95% CI, 1.30–3.24) White et al, 2008: HCV-infected patients had a significantly higher risk of diabetes compared with uninfected controls and compared with HBV-infected controls in a meta-analysis
Insulin resistance	Younossi et al, 2013: Based on NHANES data collected between 1999 and 2010, chronic HCV was independently associated with diabetes (OR, 2.31; 95% CI, 1.18–4.54), insulin resistance (OR, 2.06; 95% CI, 1.19–3.57), and hypertension (OR, 2.06; 95% CI, 1.30–3.24) Moucari et al, 2008: Insulin resistance (HOMA-IR) was present in 35% of HCV-infected vs 5% of HBV-infected patients and was associated with HCV genotypes 1 and 4, high viral load, and liver fibrosis Vanni et al, 2009: Patients with chronic HCV infection and no features of metabolic syndrome (n = 14) showed increased peripheral and hepatic insulin resistance compared with healthy controls (n = 7); hepatic insulin resistance index was increased 3-fold in HCV-infected patients compared with controls Milner et al, 2010: Insulin resistance was significantly increased in nonobese, HCV-infected male patients compared with healthy controls; insulin resistance was principally peripheral rather than hepatic, most likely in muscle Muzzi et al, 2005: HOMA-IR score was associated with fibrosis in HCV-infected patients Lecube et al, 2006: In a case-control study, HOMA-IR score was significantly higher in HCV-infected patients than in controls with chronic hepatitis other than HCV

Negro F, Gastroenterology 2015

Metabolic benefits of HCV eradication

Condition	Studies and main findings
Insulin resistance	Kawaguchi et al, 2007: Chronic HCV-infected patients treated with interferon alfa with or without ribavirin who achieved SVR had significantly reduced HOMA-IR values, whereas virological nonresponders and relapsers showed no change in HOMA-IR Milner et al, 2014: Patients with chronic HCV infection (n = 8) in whom HCV was eradicated after antiviral therapy had reduced peripheral insulin resistance compared with baseline; insulin sensitivity after viral eradication was comparable to that of matched uninfected controls Moucari et al, 2010: Decline in serum HCV RNA level was correlated with reduction in HOMA-IR score during 14 days of monotherapy with the NS3 inhibitor danoprevir, compared with HCV RNA level and HOMA-IR score which remained unchanged in patients receiving placebo
Diabetes	Arase et al, 2009: In a retrospective study, SVR after treatment with interferon or interferon plus ribavirin conferred a reduced risk (by about two-thirds) of developing type 2 diabetes mellitus, even after stratification according to age, cirrhosis, and prediabetes

Negro F, Gastroenterology 2015

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- Peripheral neuropathy

Cacoub P, DLD 2014

Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies

Study or subgroup	HCV Events	HCV Total	Control Events	Control Total	Weight	Odds ratio IV, random, 95% CI	Year
Guiltinan 2008	73	10259	34	10259	31.8%	2.16 [1.43, 3.24]	2008
Lee 2012	38	760	477	18541	34.8%	1.99 [1.42, 2.80]	2012
Vajdic 2015	59	14498	54	14048	33.4%	1.06 [0.73, 1.53]	2015
Total (95% CI)		**25517**		**42848**	**100.0%**	**1.65 [1.07, 2.56]**	
Total events	170		565				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 8.37$, df = 2 ($P = .02$); $I^2 = 76\%$

Test for overall effect: $Z = 2.25$ ($P = .02$)

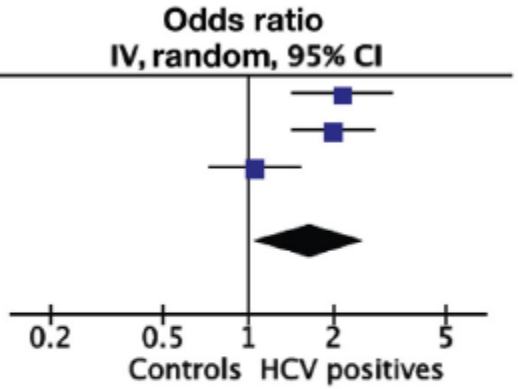

Figure 2. Meta-analysis of 3 studies that assessed the impact of HCV infection on CVD-related mortality, using the random-effects model. ORs and 95% CIs are shown on a logarithm scale. Studies are arranged by publication year. Study names are provided in the corresponding references.

Petta S, Gastroenterology 2016

Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies

A

Study or subgroup	HCV Events	HCV Total	Control Events	Control Total	Weight	Odds ratio IV, random, 95% CI	Year
Ishizaka 2002	40	104	1030	4680	20.2%	2.21 [1.48, 3.31]	2002
Ishizaka 2003	16	25	480	1967	7.8%	5.51 [2.42, 12.54]	2003
Targher 2007	22	60	9	60	7.0%	3.28 [1.36, 7.92]	2007
Bilora 2008	11	40	4	40	3.9%	3.41 [0.98, 11.85]	2008
Tien 2009	7	53	27	452	7.0%	2.40 [0.99, 5.81]	2009
Caliskan 2009	16	36	17	36	6.4%	0.89 [0.35, 2.26]	2009
Mostafa 2010	12	187	10	192	7.2%	1.25 [0.53, 2.96]	2010
Adinolfi 2012	91	326	74	477	23.1%	2.11 [1.49, 2.98]	2012
Petta 2012	73	174	40	174	17.3%	2.42 [1.52, 3.85]	2012
Total (95% CI)		**1005**		**8078**	**100.0%**	**2.27 [1.76, 2.94]**	
Total events	288		1691				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.52$, df = 8 ($P = .17$); $I^2 = 31\%$

Test for overall effect: Z = 6.25 ($P < .00001$)

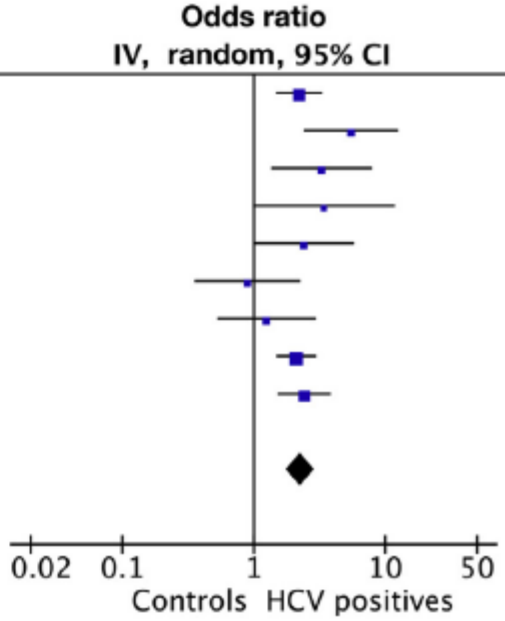

Figure 3. Meta-analysis of 9 studies that assessed the impact of HCV infection on the presence of carotid plaques, using the random-effects model. (*A*) Overall impact and (*B*) impact according to the prevalence of smoking habit in the population

Petta S, Gastroenterology 2016

Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies

A

Study or subgroup	HCV Events	HCV Total	Control Events	Control Total	Weight	Odds ratio IV, random, 95% CI	Year
Arcari 2006	23	52	269	530	5.9%	0.77 [0.43, 1.36]	2006
Butt 2009	6169	82083	5594	89582	17.8%	1.22 [1.18, 1.27]	2009
Forde 2012	16	4809	248	71668	6.9%	0.96 [0.58, 1.60]	2012
Liao 2012	482	4094	1499	16376	16.7%	1.32 [1.19, 1.48]	2012
Adinolfi 2013	33	79	90	741	7.0%	5.19 [3.15, 8.54]	2013
Hsu CS 2013	220	2875	1141	12452	15.7%	0.82 [0.71, 0.95]	2013
Enger 2014	584	21919	1456	67109	16.9%	1.23 [1.12, 1.36]	2014
Pothineni 2014	84	1434	480	14799	13.2%	1.86 [1.46, 2.36]	2014
Total (95% CI)		**117345**		**273257**	**100.0%**	**1.30 [1.10, 1.55]**	
Total events	7611		10777				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 76.44$, $df = 7$ ($P < .00001$); $I^2 = 91\%$

Test for overall effect: $Z = 3.08$ ($P = .002$)

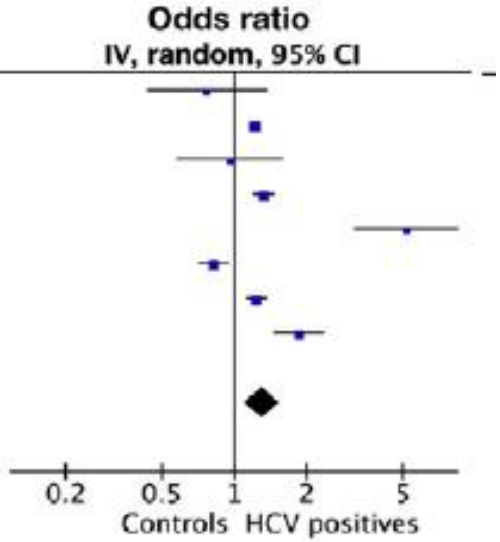

Figure 4. Meta-analysis of 8 studies that assessed the impact of HCV infection on cerebrocardiovascular events. (A

Petta S, Gastroenterology 2016

Myocardial injury in patients with chronic hepatitis C infection

Shigeo Maruyama[1], Masahiko Koda[2,*], Nobuyuki Oyake[3], Hidetoshi Sato[4], Yasuyoshi Fujii[5], Yutaka Horie[5], Yoshikazu Murawaki[2]

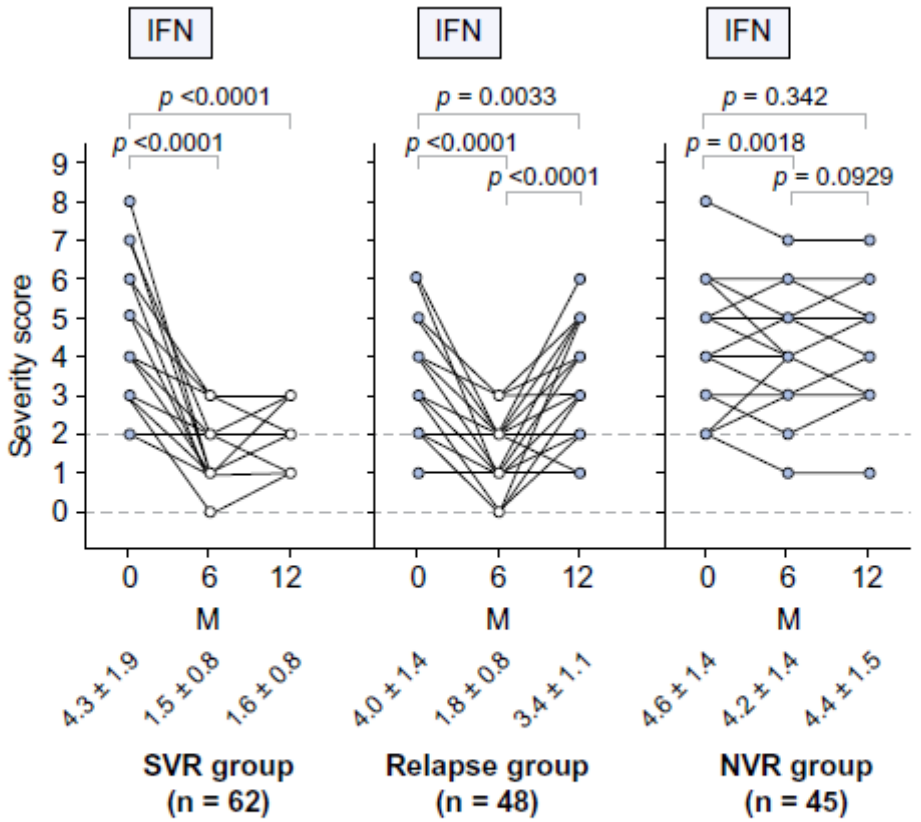

Fig. 1. Changes in the severity score of myocardial perfusion defects in SVR, relapse, and NVR groups after 24-week IFN therapy. The dotted lines indicate the normal range. Significances of individual differences were evaluated with Bonferroni's multiple comparison test.

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Maruyama S, J Hepatol 2012

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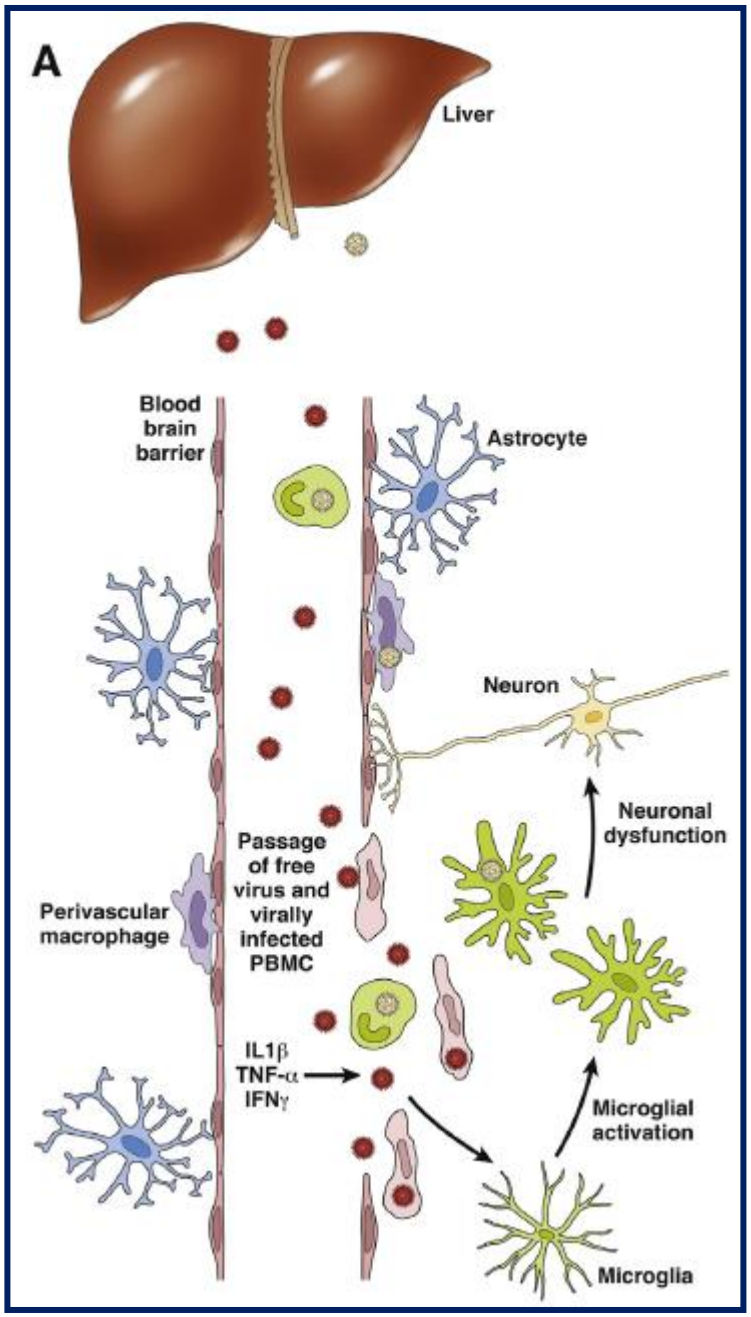
Cacoub P, DLD 2014



Negro F, Gastroenterology 2015

HCV and neurological effects

Potential effect	Studies and main findings
Fatigue	Foster et al, 1998: HCV-infected patients had significantly reduced quality of life compared with uninfected and HBV-infected controls, as measured by physical functions (fatigue, energy, body pain) assessed using the Short Form 36 symptomatology questionnaire Poynard et al, 2002: Fatigue was present in 53% of HCV-infected patients and was associated with female sex, age older than 50 years, cirrhosis, depression, and purpura Cacoub et al, 2002: Fatigue was present in 59% of patients with chronic hepatitis C Stefanova-Petrova et al, 2007: Fatigue was present in 60% of HCV-infected patients Tillmann et al, 2011: Two independent prospective cross-sectional studies of 511 and 284 patients with different forms of liver disease showed reduced mental quality of life in HCV-infected patients
Cognitive impairment	Forton et al, 2002: Patients with chronic hepatitis C who have detectable HCV RNA and histologically mild disease were cognitively impaired compared with previously infected patients who had cleared the virus and compared with healthy controls; HCV-infected patients were significantly impaired on tests of concentration and speed of memory processes Weissenborn et al, 2004: HCV-infected patients with mild liver disease showed impairment in attention and higher executive function compared with healthy controls Hilsabeck et al, 2002 and 2003: Cognitive impairment in patients with HCV was related to severity of liver disease but was also evident in patients without cirrhosis Letendre et al, 2005: HIV, HCV, and methamphetamine use were independently associated with cognitive impairment in HCV/HIV-coinfected patients Weissenborn et al, 2006: Decreased serotonin and dopamine transporter binding, measured by single-photon emission computerized tomography, was associated with impaired performance on psychometric testing Forton et al, 2008: Impairments in working memory correlated with white matter myoinositol/creatine ratios, measured by cerebral magnetic resonance spectroscopy

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Neurological benefits of HCV eradication

Condition	Studies and main findings
Fatigue and HRQOL	Cacoub et al, 2002: Achieving SVR was associated with reduction in fatigue after adjusting for age, sex, fibrosis stage, and depression (OR, 0.34; $P < .001$) Hassanein et al, 2004: HCV-infected patients who achieved SVR with peginterferon plus ribavirin or interferon alfa plus ribavirin had significant improvement in HRQOL, as assessed by the SF-36 and FSS Rasenack et al, 2003: HCV-infected patients who achieved SVR after 48 weeks of peginterferon or interferon alfa therapy had significantly improved HRQOL compared with those without SVR, as measured by mean SF-36 scores and mean FSS scores Younossi et al, 2014: Patients infected with HCV genotype 2 or 3 who were treated with sofosbuvir and ribavirin and achieved SVR had significant improvements from baseline in HRQOL, as measured by fatigue, SF-36 score, emotional well-being, general health, and results of the Chronic Liver Disease Questionnaire-HCV
Cognitive function	Kraus et al, 2013: HCV-infected patients with SVR after treatment with peginterferon and ribavirin showed significant improvement in neurocognitive function when tested at least 1 year after the end of therapy; patients without SVR showed no changes in neurocognitive function
Cerebral magnetic resonance spectroscopy	Alsop et al, 2014: After treatment with ledipasvir-sofosbuvir, patients with HCV showed increases in cerebral *N*-acetylaspartate levels, interpreted as recovery of neuronal dysfunction
MC	Gragnani et al, 2015: HCV-infected patients with MC treated with peginterferon and ribavirin showed a good clinicoimmunologic correlation with SVR, because all patients with SVR also experienced a sustained clinical response, either complete or partial, whereas all virological nonresponders were also clinical nonresponders, despite a transient improvement in some patients Saadoun et al, 2015: 30 patients with hepatitis C and MC, mostly previous nonresponders, were re-treated with peginterferon and ribavirin plus a protease inhibitor (telaprevir or boceprevir), with a high rate of both clinical and virological success despite adverse effects

Negro F, Gastroenterology 2015

Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition

Valerie Byrnes[1], Anne Miller[2], Damien Lowry[4], Erin Hill[2], Cheryl Weinstein[2], David Alsop[3], Robert Lenkinski[3], Nezam H. Afdhal[1,*]

Background & Aims: Chronic hepatitis C virus (HCV) infection is associated with altered cerebral metabolism and cognitive dysfunction. We aimed to evaluate the effect of pegylated interferon/ribavirin (PIFN/R) and HCV clearance on cerebral metabolism, and neuropsychological performance.

Methods: Fifteen non-cirrhotic HCV positive subjects underwent ^{1}H MR spectroscopy (MRS) before, during, and after treatment with PIFN/R. The metabolites of interest namely, *N*-acetylaspartate (NAA), choline (Cho), myo-inositol (MI), and the control metabolite creatine (Cr), were acquired from 3 different brain regions; left basal ganglia, left frontal cortex, and left dorso-lateral pre-frontal cortex. Coinciding with this, subjects also underwent a battery of neuropsychological tests to evaluate the domains of verbal learning, memory, attention, language, executive functioning, and motor skills. Seven HCV positive controls (not receiving anti-viral therapy) underwent MRS and neuropsychological testing at two time points, 12 weeks apart, to examine for variation in cerebral metabolites over time and the practice effect of repeat neuropsychological testing.

Results: Significant reductions in basal ganglia Cho/Cr ($p = 0.03$) and basal ganglia MI/Cr ($p = 0.03$) were observed in sustained virological responders (SVRs, n = 8), but not non-responders/relapsers (NR/R, n = 6), indicative of reduced cerebral infection and/or immune activation in those who cleared virus. SVRs demonstrated significant improvements in verbal learning, memory, and visuo-spatial memory. A small but significant improvement in neurocognitive function secondary to the practice effect was seen in both HCV controls and HCV subjects during treatment.

Conclusions: HCV eradication has a beneficial effect on cerebral metabolism and selective aspects of neurocognitive function and is an important factor when contemplating anti-viral therapy in HCV, especially in those with mild disease.

J Hepatol 2012

Main extra epatic manifestations of HCV according to the strenght of the association

A. Significant prevalence, consistent pathogenetic data and "ex-adjuvantibus" criteria
- Mixed cryoglobulinaemia/cryoglobulinaemic vasculitis
- B-cell NHL

B. Higher prevalence than controls
- Type 2 diabetes mellitus type 2
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Cardiovascular disorders (i.e. stroke, ischemic heart disease)
- Sicca syndrome
- Arthralgia/myalgia
- Auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)
- Monoclonal gammopathies
- Immune thrombocytopenia
- Porphyria cutanea tarda
- Lichen planus

C. Possible association
- Polyarthritis
- Pruritus
- Fibromyalgia
- Chronic polyradiculoneuropathy
- Lung alveolitis

D. Anecdotal association
- Polymyositis
- Dermatomyositis
- Polyarteritis nodosa
- Psoriasis
- Mooren corneal ulcer
- Erythema nodosum

E. Association with antiviral treatment (interferon alpha)
- Hypo-hyperthyroidism
- Depression
- Fatigue
- Impaired quality of life
- Sarcoidosis
- Lichen
- Skin vasculitis
- Peripheral neuropathy

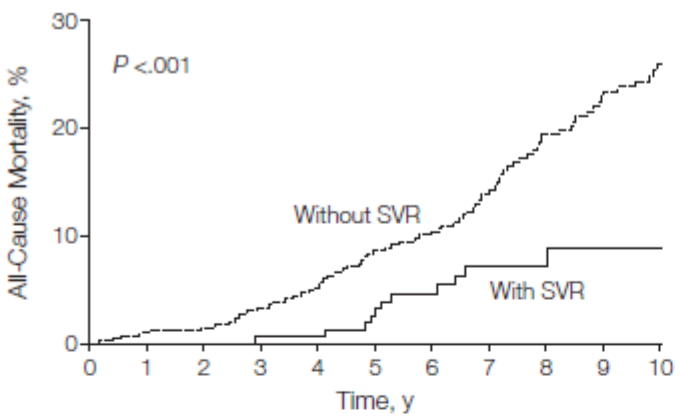
Cacoub P, DLD 2014

Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis

An international, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada of 530 patients with chronic HCV infection who started an interferon-based treatment regimen between 1990 and 2003, following histological proof of advanced hepatic fibrosis or cirrhosis (Ishak score 4-6).
Complete follow-up ranged between January 2010 and October 2011

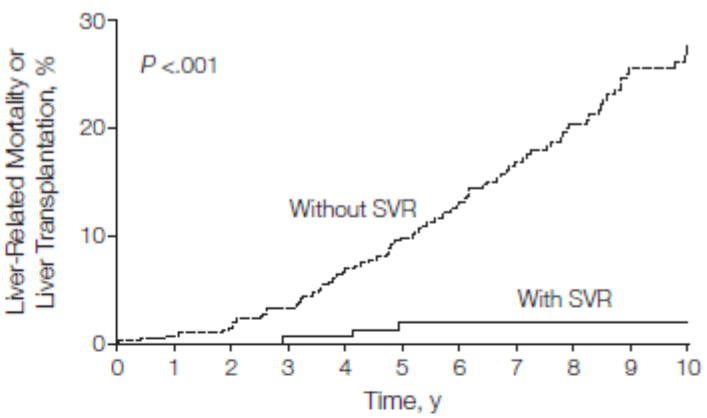
van der Meer, JAMA 2012

Association Between Sustained Virological Response and All-Cause Mortality Among Patients With Chronic Hepatitis C and Advanced Hepatic Fibrosis



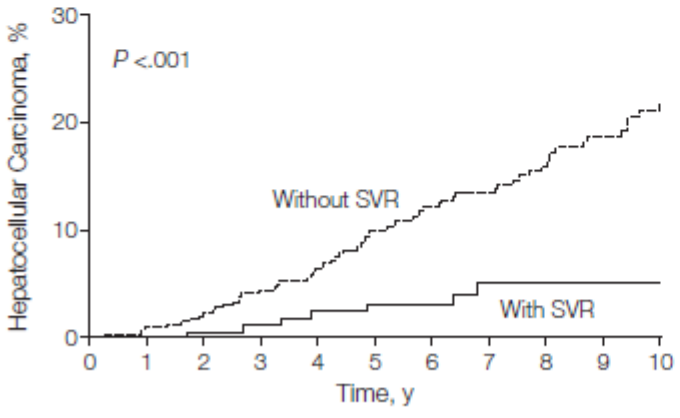
No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



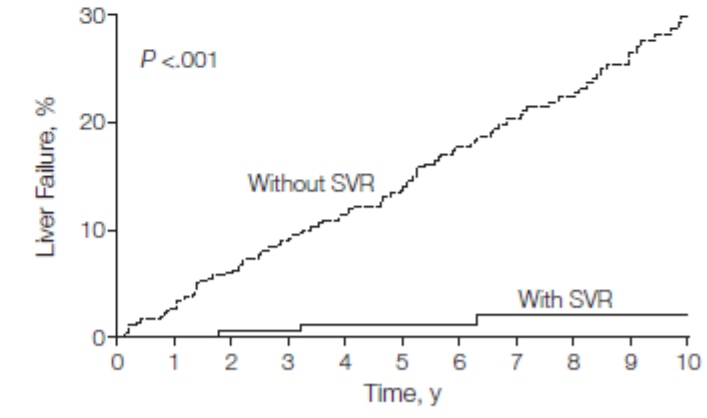
No. at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28



No. at risk

Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27



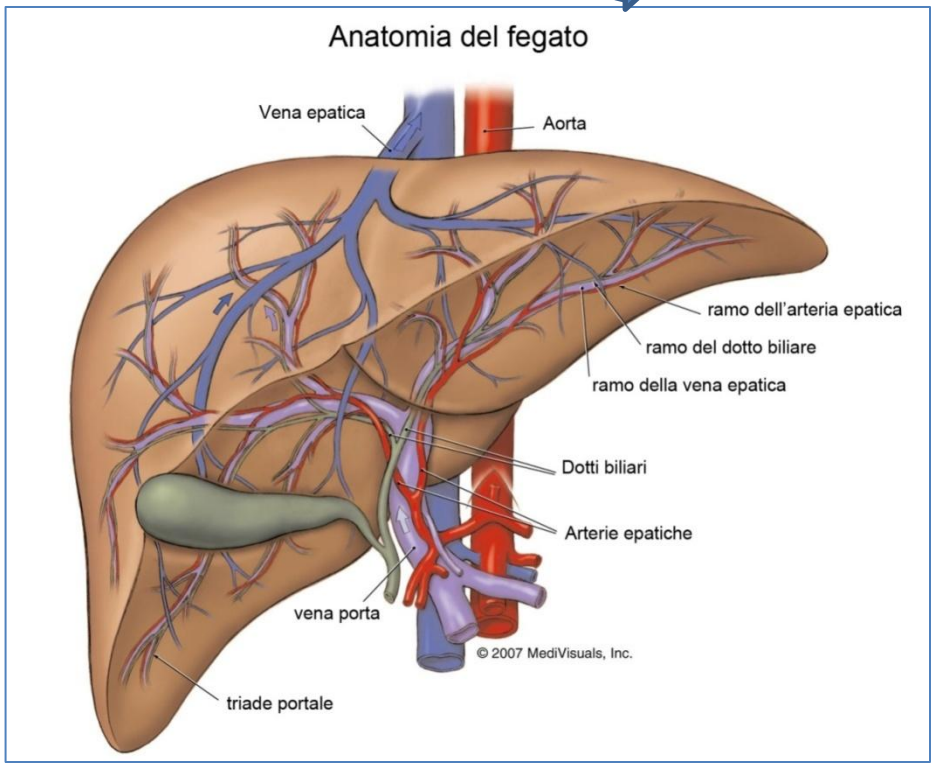
No. at risk

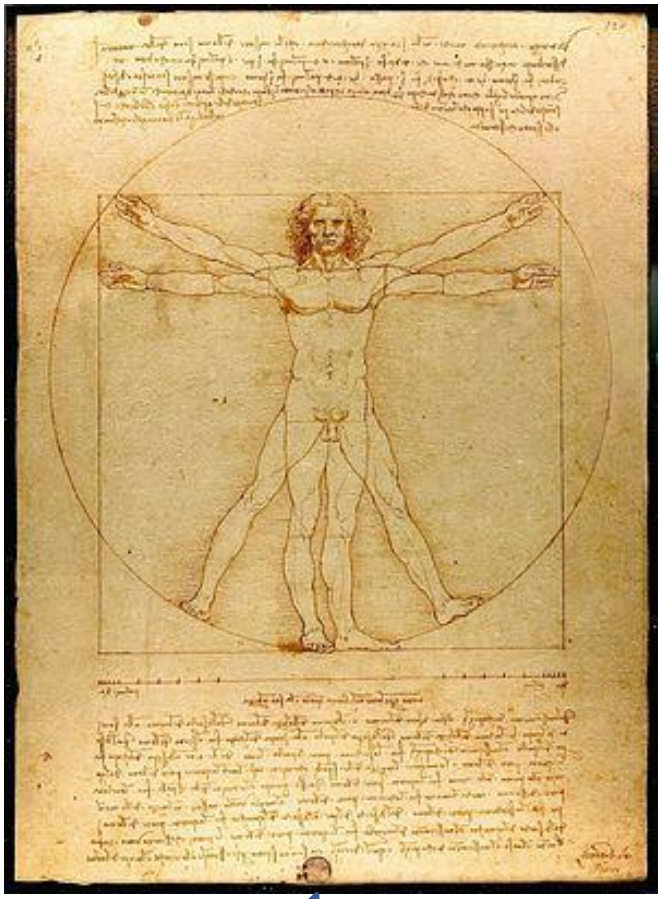
Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

van der Meer, JAMA 2012

Conclusions

HCV infection





anti-HCV treatment effects

Background

The implication of the endocannabinoid system was suggested in several diseases:

- cardiovascular diseases
- metabolic diseases
- gastrointestinal diseases
- nervous system diseases
- cancer
- …

Di Marzo V, Drug Discover 2005
Patel KD, Curr Med Chem 2010
Petwee RG, Pharmacol Rev 2010
Rossi F. Pharmacol Res 2012

Pacher P, Pharmacol Rev, 2006
Klein TW, Nat Rev Immunol 2005
Rossi F. Haematologica 2011