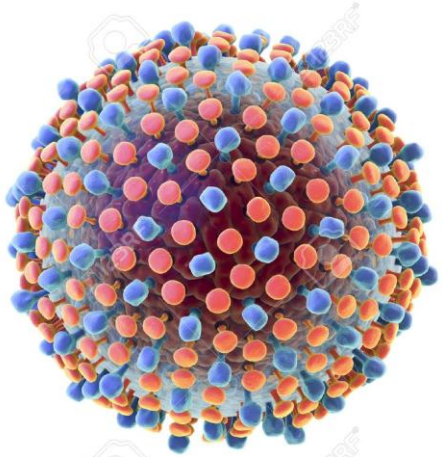
ORDINE MEDICI CHIRURGHI E ODONTOIATRI DELLA PROVINCIA DI BRESCIA



BRESCIA, 18 MAGGIO 2018

LA SINDROME DA HCV. LE MANIFESTAZIONI EXTRAEPATICHE: differenze di genere.

CONOSCERE L'EPATITE C: SCREENING DIAGNOSI E CLINICA

SILVIA ODOLINI
Clinica Malattie Infettive e Tropicali
ASST Spedali Civili di Brescia

Disclosures

- Speaker’s grant: MSD, Bristol Myers Squibb, Abbvie, Gilead;

- No conflicts of interest pertaining to subject matter of this talk.

Considering hepatitis C virus infection as a systemic disease

Patrice Cacoub[1,2,3,4] | Cloé Comarmond[1,2,3,4]

Semin Dial. 2019 Mar;32(2):99 - 107

- HCV is recognized as one of the hepatic viruses most often associated with extrahepatic manifestations (EHMs), which present in up to two-thirds of infected patients.

- Extrahepatic syndromes may represent the first signal of HCV infection in some patients.

- Several of these manifestations are common and well-described while others are less frequent.

Table 1. Main extrahepatic manifestations in patients with hepatitis C virus infection.

Immune-related extrahepatic manifestations
Mixed cryoglobulinemia
Cryoglobulinemic vasculitis
B-cell NHL
Sicca syndrome
Arthralgia/myalgia
Autoantibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies)
Polyarteritis nodosa
Monoclonal gammopathies
Immune thrombocytopenia
Inflammatory-related extrahepatic manifestations
Type 2 diabetes mellitus type 2
Insulin resistance
Glomerulonephritis
Renal insufficiency
Fatigue
Cognitive impairment
Depression
Impaired quality of life
Polyarthritis/fibromyalgia
Cardiovascular disorders (i.e. stroke, ischemic heart disease)

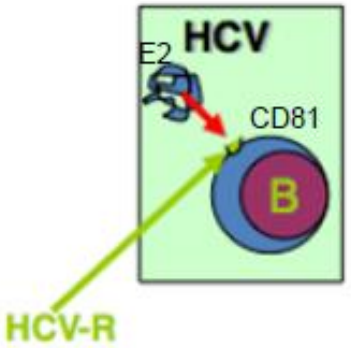
NHL, non-Hodgkin's lymphoma.

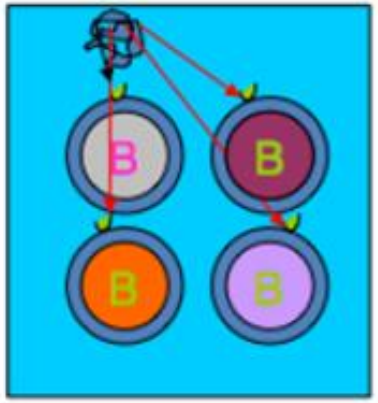
Cacoub et al., Ther Adv Infect Dis 2016

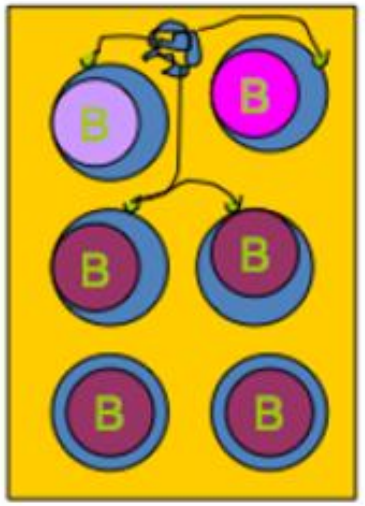
Cosa c’è alla base delle manifestazioni extraepatiche da HCV?

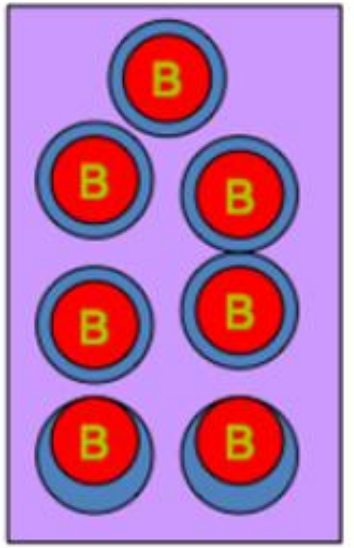
- Nel 20-40% dei casi di infezione da HCV sono presenti autoanticorpi non organo specifici;
- I linfociti B dei pazienti con infezione da HCV sono stimolati a produrre Ig attraverso l’interazione di varie molecole linfocitarie e virali;
- Attivazione policlonale B con produzione di autoanticorpi diretti contro autoepitopi tissutali e immunoglobulinici (es. crioglobulinemia tipo III);
- Rimane da interpretare la comparsa di autoanticorpi monoclonali (crioglobulinemia tipo II, comparsa di IgG e IgM sieriche monoclonali).

AISF, 2003









Cellula B Attivata da HCV

Espansione Policlonale

Autoantic.

ANA-SMA

Crioglobul.III°

Espansione Oligoclonale

MLDUS

Autoaanticorpi Monoclonali: FR

Crioglobilinemia II°

Riarr. BCl-2

Espansione Monoclonale

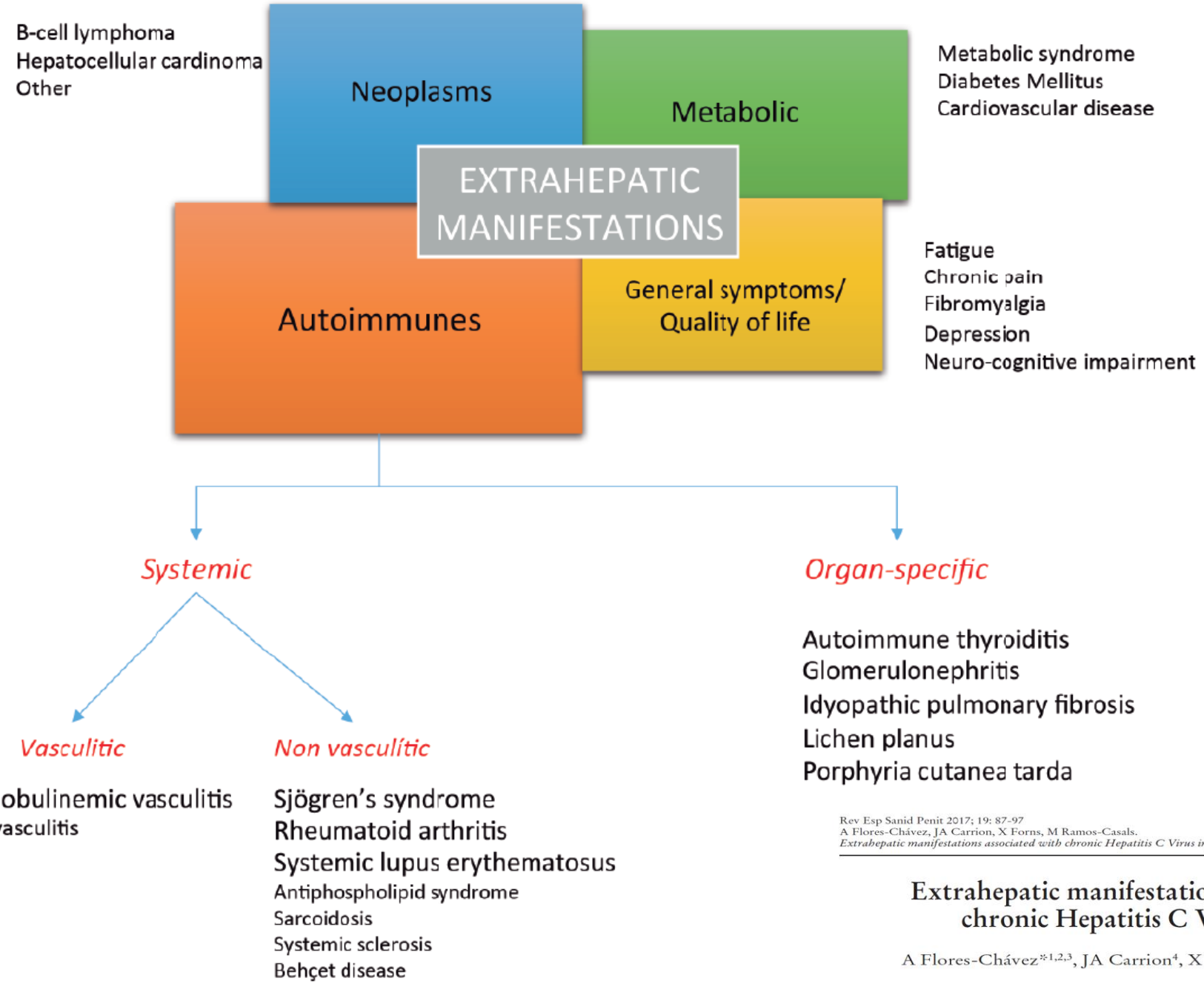
LinfomaNon HG

Traslocazione t

(14-18)

E 2+CD81(CD19-CD21)

> Ricomb.V(D)J



Rev Esp Sanid Penit 2017; 19: 87-97
A Flores-Chávez, JA Carrion, X Forns, M Ramos-Casals.
Extrahepatic manifestations associated with chronic Hepatitis C Virus infection

Extrahepatic manifestations associated with chronic Hepatitis C Virus infection

A Flores-Chávez*[1,2,3], JA Carrion[4], X Forns[5], M Ramos-Casals[1,6]

Figure 1. Classification of extrahepatic manifestations associated with chronic HCV infection.

Outline of presentation

- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
- Insulin resistance
- Neurocognitive disorders

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- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
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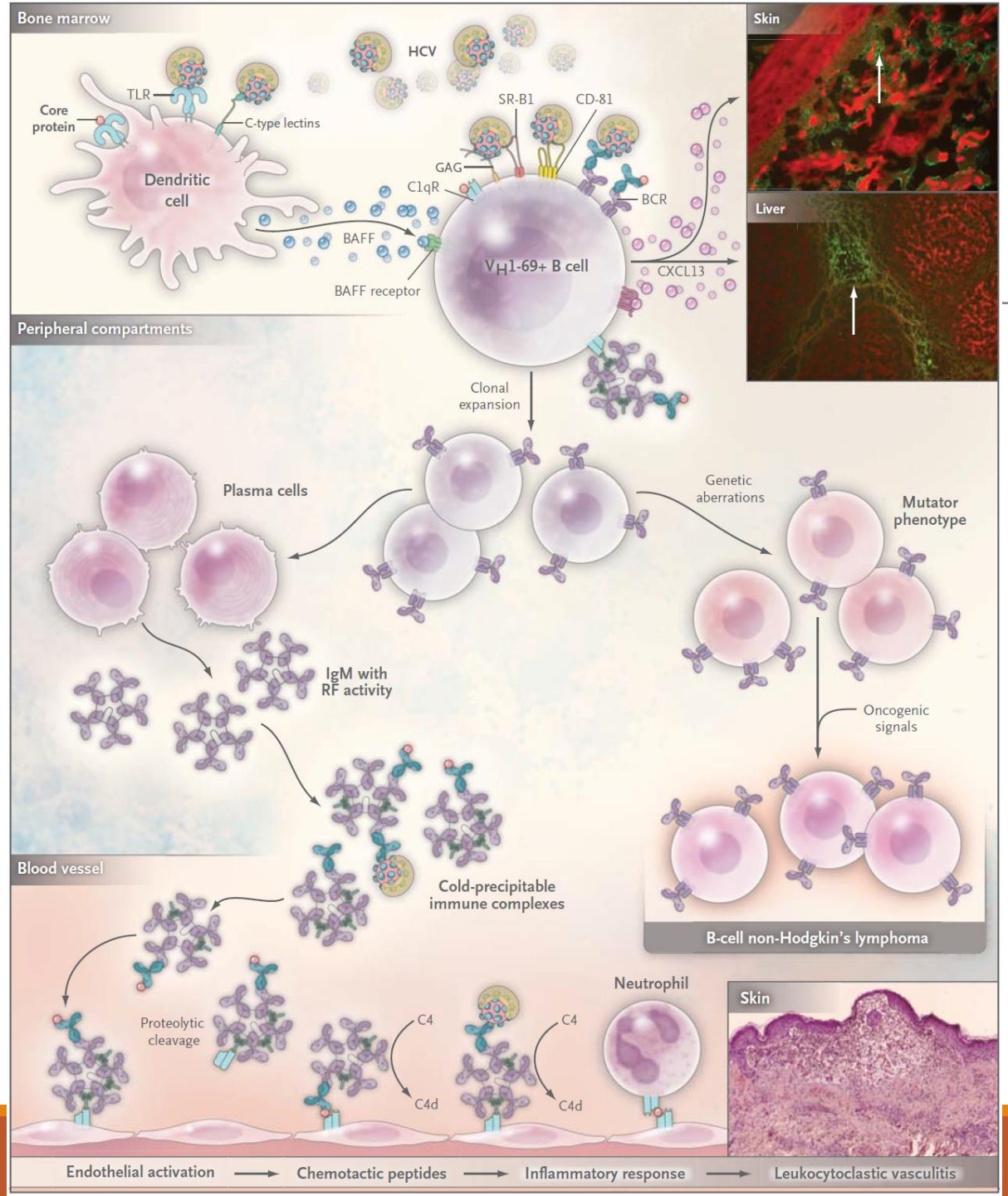
CRYOGLOBULINEMIC VASCULITIS

- **Cryoglobulins are immunoglobulines characterized by their insolubility at low temperatures (< 37°C) and their dissolution after rewarming.**
- Cryoglobulins classification (Brouet et al.,):
  - **type I** (composto da una Ig monoclonale)
  - **type II e III (CMII e CMIII)** (caratterizzati da IgG policlonali ed IgM ad attività di fattore reumatoide, rispettivamente monoclonali e policlonali)
- **L'infezione da HCV è spesso associata alla crioglobulinemia di tipo II**
- **Cryoglobulins can be detected in 40-60% of HCV positive patients**
- Cryoglobulin-related illness, known as **cryoglobulinemic vasculitis,** appears in a minority (10 to 15%) of patients and include a spctrum of symptoms ranging from mild to life-threatening.CA

Dammaco et al., N Engl J Med 2013: 369:1035-45
AISF, 2003



After recognition receptors link with HCV, dendritic cells release B cells- activating factor (BAFF) of the tumor necrosis family

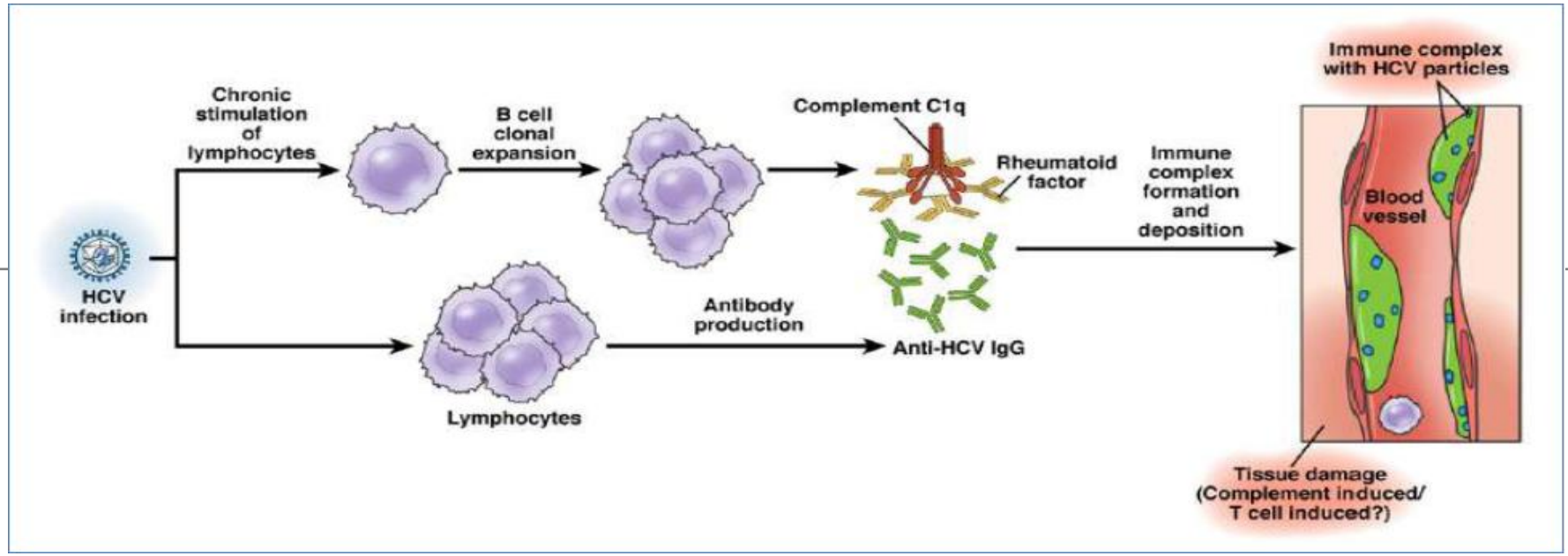
B cells capture HCV particles and are highly responsive to BAFF → clonal expansion of B cells

These cells synthetize large amounts of IgM with rheumatoid factor (RF) activity

IgM RF molecules bind HCV particles resulting in the formation of cold precipitable multimolecular Immune complexes

The impaired regulatory control of B cell growth supports an antigen-driven stimulation model in which aberrant B-cell variants potentially evolve into B-cell non Hodgkin's lymphoma.

Dammaco et al., N Engl J Med 2013: 369:1035-45.

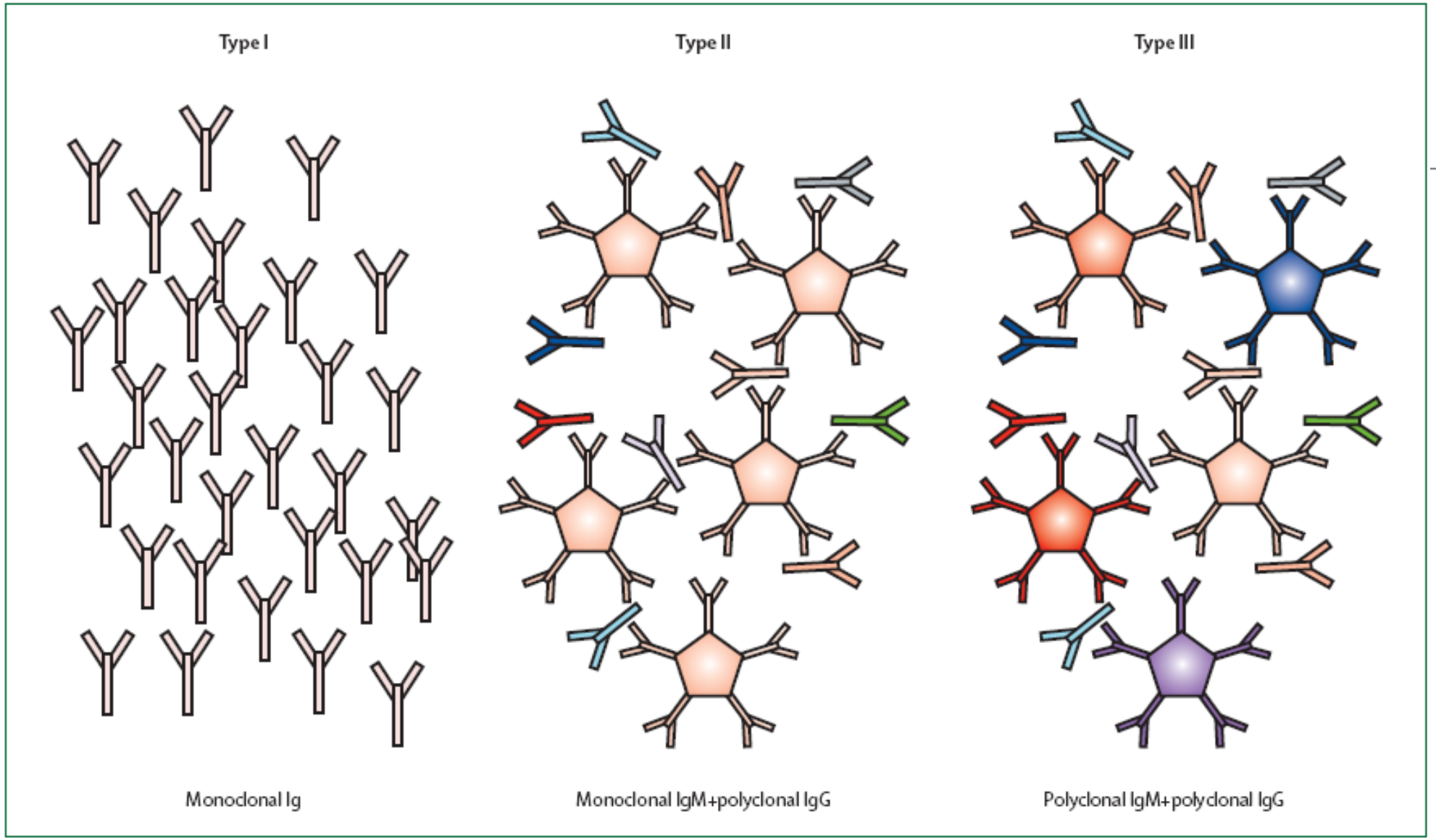


Due principali meccanismi patogenetici di danno vascolare:

1 . **Precipitazione crioglobuline nel microcircolo** con conseguente occlusione vascolare (più frequente in crioglobulinemia tipo I);

2 . **Infiammazione vasi mediata da immuno-complessi** (più frequente nelle crioglobulinemia miste, soprattutto di tipo II, dove IgM monoclonali formano larghi immunocomplessi).

Ramos-Casals et al., Lancet 2012


Type I
Type II
Type III
Monoclonal Ig
Monoclonal IgM+polyclonal IgG
Polyclonal IgM+polyclonal IgG

	Most frequent causes	Less frequent causes	Infrequent causes
Infections	Hepatitis C virus	HIV; Hepatitis B virus	*Streptococcus* spp; *Brucella* spp; *Coxiella* spp; *Klebsiella* spp; *Leishmania* spp; *Chlamydia* spp; *Mycobacterium tuberculosis*; leprosy; hepatitis A virus; cytomegalovirus; parvovirus B-19; chikungunya virus; Epstein-Barr virus; hantavirus; plasmodium; amoebaiasis; toxoplasmosis
Autoimmune diseases	Sjögren's syndrome	Systemic lupus erythematosus; Rheumatoid arthritis	Systemic sclerosis; antiphospholipid syndrome; inflammatory myopathies; adult-onset Still's disease; polyarteritis nodosa; giant-cell arteritis; Takayasu's arteritis; ANCA-associated vasculitis; autoimmune hepatitis
Cancer	B-cell lymphoma	Multiple myeloma	Hodgkin's lymphoma; chronic lymphocytic leukaemia; chronic myeloid leukaemia; myelodysplasia; hepatocellular carcinoma; papillary thyroid cancer; lung adenocarcinoma; renal cell carcinoma; nasopharyngeal carcinoma
Other causes	..	Alcoholic cirrhosis	Co-trimoxazole;* interferon alfa;* cocaine;* intravenous radiographic contrast;* influenza vaccination; hepatitis B vaccination; intravesical BCG; moyamoya disease; endocarditis; chilblains

ANCA=antineutrophil cytoplasmic antibodies. *Associated with cryoglobulinaemic exacerbation.

Table: **Main causes associated with cryoglobulinaemia since 1990[23]**

- Cryoglobulinemic vasculitis is associated with **older age, longer duration of HCV infection, MC type II and high levels of serum cryoglobulins** (Sene et al.)

- The activity of HCV-associated cryoglobulinemic vasculitis generally correlate with viremia

Florez-Chavez et al., 2013

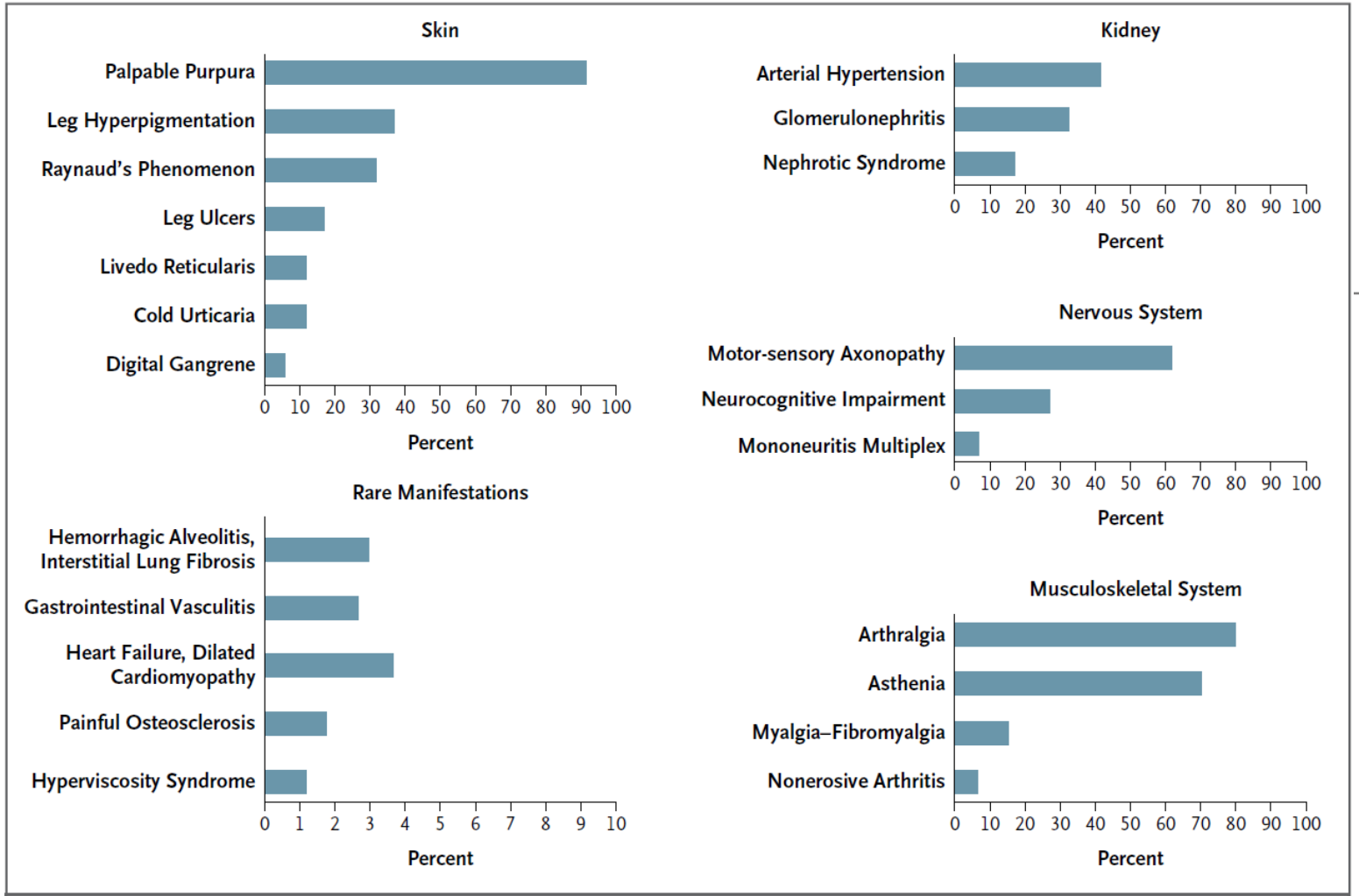


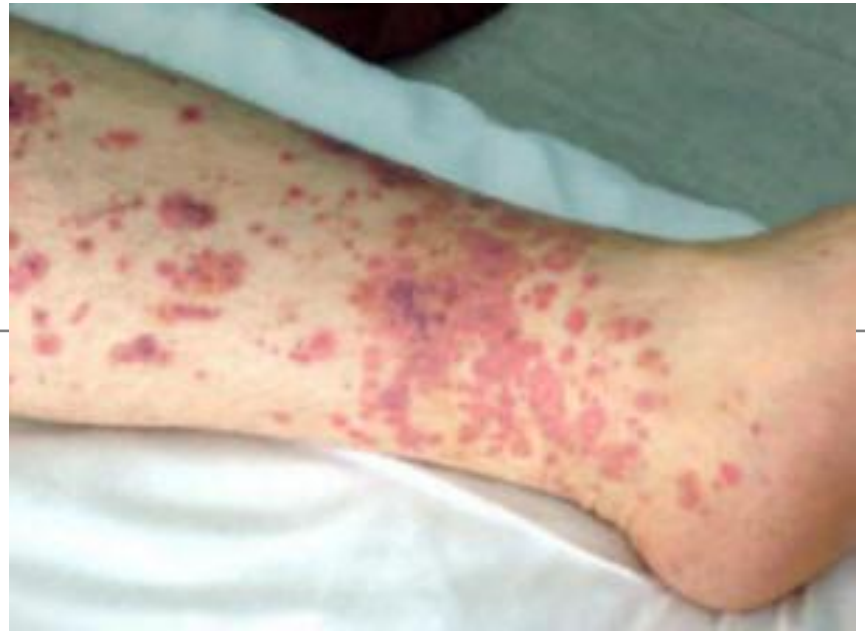
Figure 2. Spectrum of Clinical Features in Patients with HCV-Related Cryoglobulinemic Vasculitis.

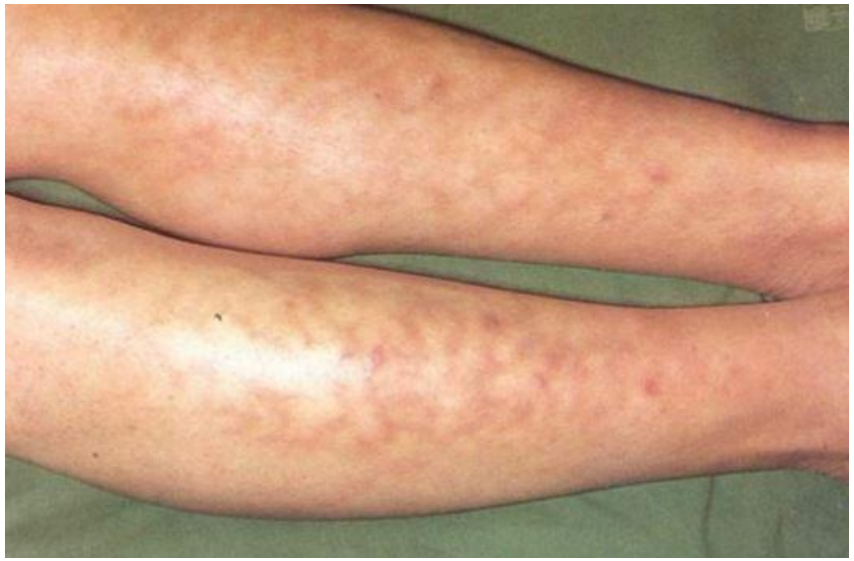
The percentages reflect our experience in treating 246 patients with chronic HCV infection and cryoglobulinemic vasculitis. The pathogenesis of rare manifestations is unclear. Hemorrhagic alveolitis may be due to vasculitis that involves small arteries, capillaries, and venules, resulting in interstitial lung fibrosis.[11] Small- and medium-vessel vasculitis accounts for gastrointestinal involvement.[12] Cryoglobulinemic vasculitis–induced cardiomyopathy probably reflects myocardial vessel disease; an association with B-cell non-Hodgkin's lymphoma and severe clinical manifestations has been recognized.[13] HCV-associated osteosclerosis may be caused by an imbalance of the osteoprotegerin–receptor activator of the nuclear factor κB ligand system.[14] Finally, a hyperviscosity syndrome, which is most frequent in type I cryoglobulinemia, develops as a product of the formation of macromolecular cryoprecipitating complexes.[15]

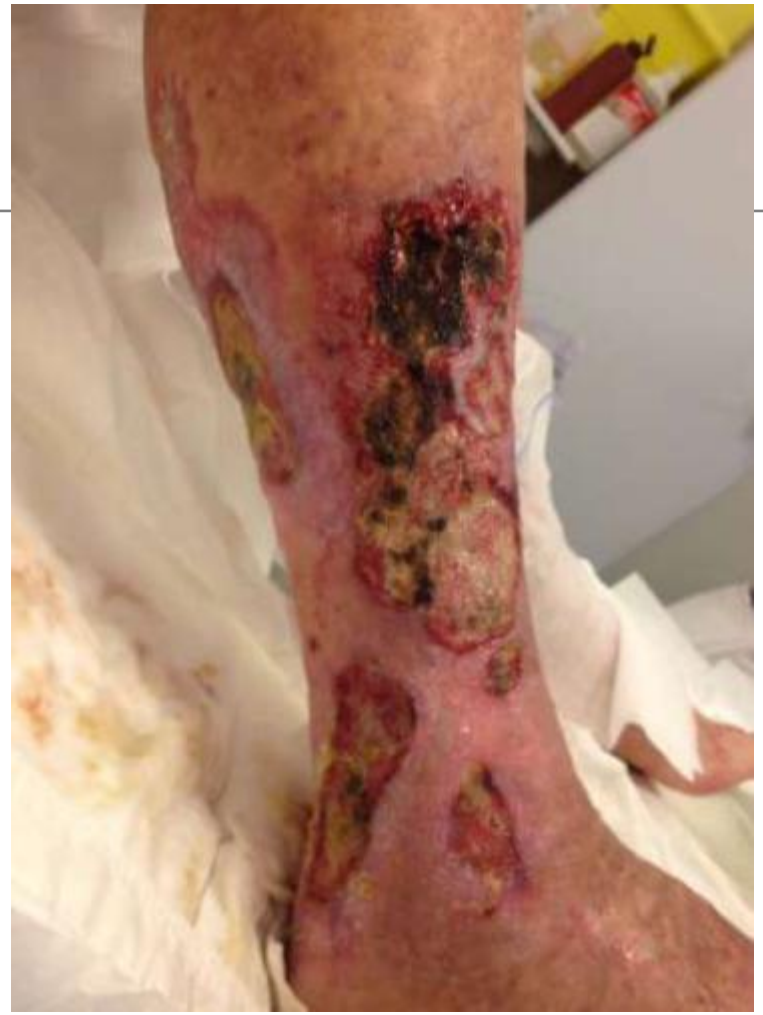
TYPICAL (>80%) TRIAD at ONSET:

1. PURPURA
2. WEAKNESS
3. ARTHRALGIA

Dammaco et al., N Engl J Med 2013: 369:1035-45.
Passerini et al., Eur J Gastroenterol Hepatol. 2018; 30(10):1208-1215.







Ulcera vasculitica

Natural History and Clinical Impact of Cryoglobulins in Chronic Hepatitis C: 10-Year Prospective Study of 343 Patients

GASTROENTEROLOGY 2007;133:835–842

MAURO VIGANÒ,* PIETRO LAMPERTICO,* MARIA GRAZIA RUMI,* CHRISTIAN FOLLI,‡ LORENA MAGGIONI,§ ALBERTO MORABITO,¶ ERSILIO DEL NINNO,* MARCO CICARDI,§ and MASSIMO COLOMBO*

- Studio prospettico
- 3 obiettivi:

1. definire la prevalenza e incidenza di CGs e il loro impatto sullo sviluppo di manifestazioni extraepatiche e outcome dell'HCV (cirrosi, HCC, scompenso epatico);

2. definire la comparsa di nuova complicanza extraepatica ogni 6 mesi;

3. definire l'overall survival.

Table 1. Demography and Clinical Characteristics of the 343 Patients at the Time of Enrollment in the Study According to the Presence or Absence of Serum CGs

Features	All patients (n = 343)	CG (+) (n = 163)	CG (−) (n = 180)	*P* value
Females, *n*	170 (50%)	99 (61%)	71 (40%)	.0002
Median age, y (*range*)	58 (22–76)	58 (22–74)	59 (22–76)	NS
Median ALT level, IU/mL (*range*)	88 (62–657)	88 (62–657)	89 (65–332)	NS
Histologic staging[a]				
0–2	159 (46%)	66 (41%)	93 (52%)	
3–4	102 (30%)	49 (30%)	53 (29%)	
5–6	82 (24%)	48 (29%)	34 (19%)	.04[b]
Genotype 1 HCV, n	162 (58%)	71 (58%)	91 (58%)	NS
Non-1 HCV genotype, n	115 (42%)	58 (42%)	57 (42%)	NS
Median duration of liver disease, y (*range*)	11 (1–42)	11 (1–42)	10 (1–42)	NS
Cryoglobulinemic syndrome, n	5 (1.5%)	5 (3%)	0 (0%)	NS
Median follow-up period, mo (*range*)	116 (17–130)	115 (17–127)	116 (22–130)	NS

[a]Ishak score.
[b]Stage 5–6 vs 0–4.

Table 5. Clinical Outcome of 343 Patients According to the Presence or Absence of CGs at Enrollment

Outcomes	All patients (n = 343)	CG (+) (n = 163)	CG (−) (n = 180)
HCC, n	33 (10%)	19 (12%)	15 (8%)
Clinical decompensation, n	23 (7%)	13 (8%)	11 (6%)
Non-Hodgkin's lymphoma, n	1 (.3%)	1 (.6%)	0 (0%)
Extrahepatic autoimmune disease, n	13 (4%)	8 (5%)	5 (3%)
Liver-related death, n	36 (10%)	21 (13%)	15 (8%)
Non–liver-related death, n	16 (5%)	8 (5%)	8 (4%)

NOTE. Patients were followed up for 116 months (range, 17–130 mo).
P value = NS for all comparisons.

Treatment of HCV-associated MC vasculitis targets

- HCV viral trigger
- downstream pathogenic events by means of less specific approaches, such as corticosteroids, immunosuppressants, or plasmapheresis

Saadoun et al., 2006

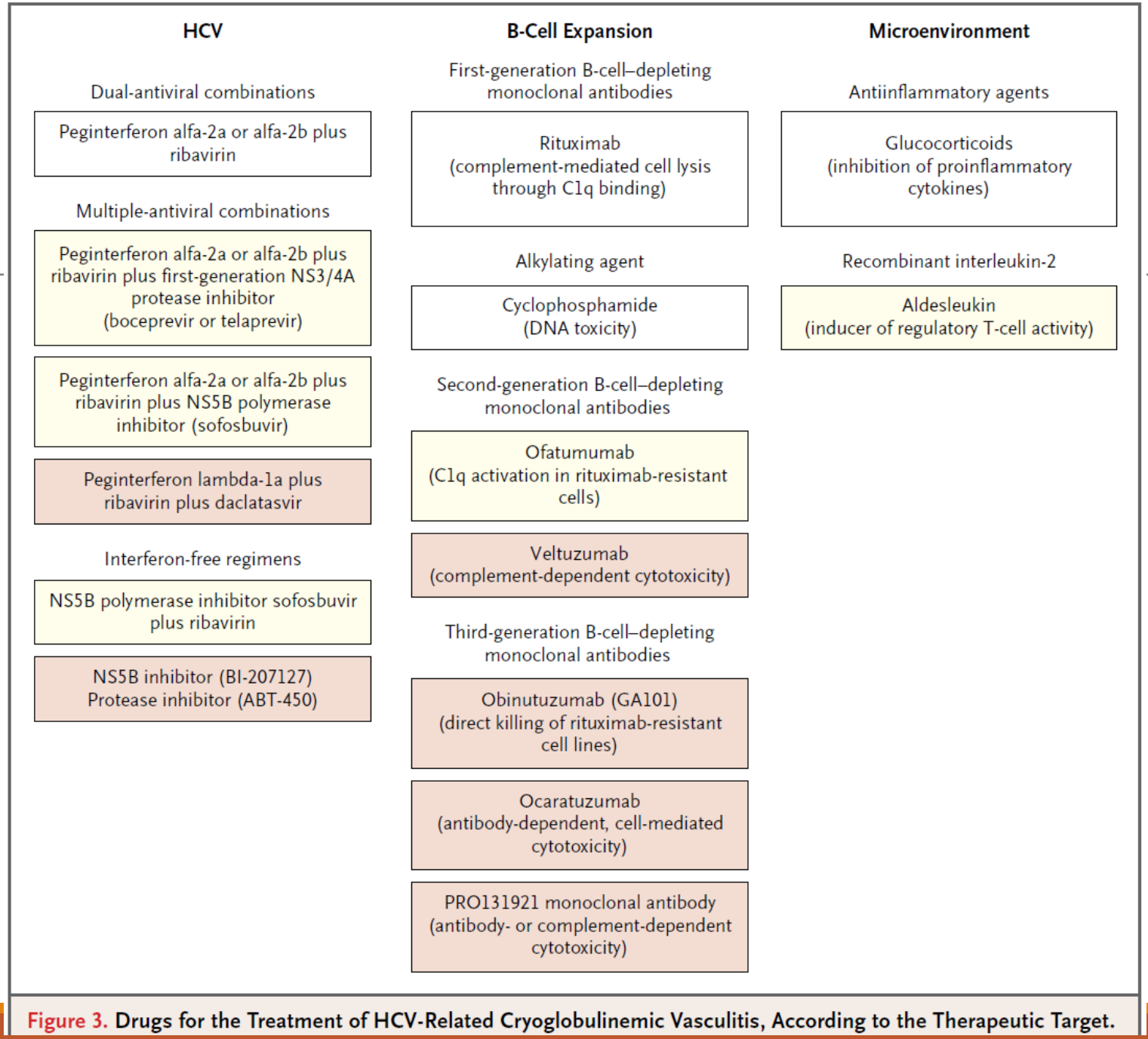
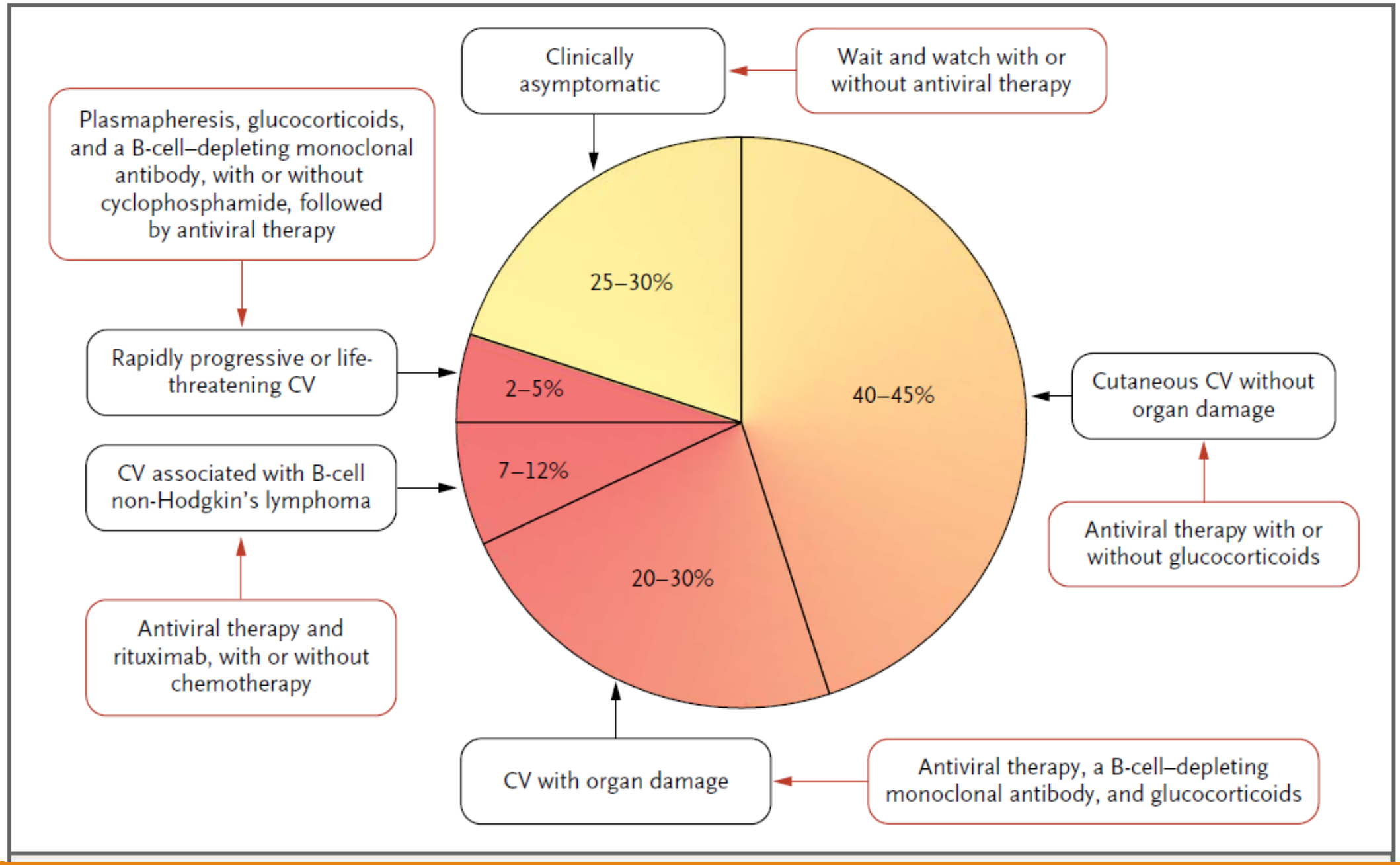


Figure 3. Drugs for the Treatment of HCV-Related Cryoglobulinemic Vasculitis, According to the Therapeutic Target.

Dammaco et al., N Engl J Med 2013: 369:1035-45.



Dammaco et al., N Engl J Med 2013: 369:1035-45.

Are direct-acting antivirals safe and effective in hepatitis C virus-cryoglobulinemia? virological, immunological, and clinical data from a real-life experience

Matteo Passerini[a], Monica Schiavini[a], Carlo F. Magni[a], Simona Landonio[a], Fosca Niero[a], Simone Passerini[a], Alessandro L. Croci[a], Matteo Bolis[a], Valentina Scalzi[b], Guido Gubertini[a], Elena D. Ricci[d], Massimo Galli[c] and Giuliano Rizzardini[a]

- Real-life observational cohort study of patients with MC (naive or non responder to P/R) who received DAA treatment from feb 2015 to Nov 2016
- Primary aim: evaluate efficacy and safety of DAAs
- Secondary aim: evaluate efficacy of DAAs in the clinical and immunological remission of mixed cryoglobulinemia

Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215

Table 1. Baseline characteristics

	Cryoglobulinemic patients			
	Symptomatic	Asymptomatic	Noncryoglobulinemic patients	*P*-value
Patients (*N*)	35	60[a]	89	
Male [*n* (%)]	11 (31.4)	26 (43.3)	36 (40.4)	0.51
Female [*n* (%)]	24 (68.6)	34 (56.7)	53 (59.6)	
Age [mean (SD)]	67 (12.7)	61.6 (15.4)	63.6 (14)	0.24
BMI [mean (SD)]	24 (3)	24 (3.6)	26 (4.2)	0.06
Cirrhosis [*n* (%)]	14 (40)	18 (30)	41 (46.1)	0.51
eGFR[b] [mean (SD)]	87 (23.6)	93.3 (24.4)	102.4 (26.4)	0.003
HCV-RNA [median (IQR)] (UI/ml)	267 598 (51 997–709 662)	394 828 (113 618–863 458)	512 166 (134 866–1 454 075)	0.11
ALT [median (IQR)] (IU/l)	46 (27–84)	55 (42.5–102)	76 (44–122)	0.005
Fibroscan [median (IQR)] (kPa)	7.8 (5.8–16.1)	8.5 (5.3–14.3)	12 (10.2–17.1)	0.0005
Genotypes [*n* (%)]				0.88
1a	1 (2.9)	4 (6.7)	7 (7.9)	
1b	14 (40)	18 (30)	33 (37.1)	
1nd	2 (5.7)	6 (10)	4 (4.5)	
2	12 (34.3)	17 (28.5)	25 (28.1)	
3	2 (5.7)	8 (13.3)	9 (10.1)	
4	4 (11.4)	7 (11.7)	11 (12.4)	
Treatment naive [*n* (%)]	27 (77.1)	45 (75)	59 (66.3)	0.35
Regimens [*n* (%)]				0.99
With RBV	19 (54.3)	28 (46.7)	45 (50.5)	
2D-R	1 (2.8)	3 (5)	4 (4.5)	
3D-R	3 (8.6)	5 (8.3)	8 (9)	
HARVONI-R	4 (11.4)	4 (6.6)	8 (9)	
SOF-R	8 (22.8)	13 (21.6)	19 (21.3)	
SOF-DAC-R	2 (5.7)	1 (1.6)	3 (3.4)	
SOF-SIM-R	1 (2.8)	2 (3.3)	3 (3.4)	
Without RBV	16 (45.7)	32 (53.3)	44 (49.5)	
3D	4 (11.4)	12 (20)	16 (18)	
SOF+LED	6 (17.1)	4 (6.6)	10 (11.2)	
SOF-DAC	4 (11.4)	13 (21.6)	13 (14.6)	
SOF-SIM	2 (5.7)	3 (5)	5 (5.6)	

Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215

Table 2. Efficacy and safety of direct-acting antivirals

	Cryoglobulinemic patients			
	Symptomatic	Asymptomatic	Noncryoglobulinemic patients	*P*-value
Virologic response [*n* (%)]				
SVR	35 (100)	57 (95)	83 (93.3)	0.29
Relapse	0	2 (3.3)[a]	0	
Stopped for AE	0	0	1 (1.1)[b]	
Death during the regimens	0	1 (1.7)[c]	1 (1.1)[d]	
Lost to FU	0	0	4 (4.5)	
AE [*n* (%)]	20 (57.1)	32 (53.3)	43 (48.3)	0.64
AE (*N*)				
Anemia	10	9	20	0.29
Jaundice	0	2	5	
Rash	1	3	3	
Asthenia	10	9	16	
Neurologic	3	7	9	
Itch	7	3	7	
Gastrointestinal	9	11	10	
Other	6	3	1	

AE, adverse events; FU, follow-up; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.

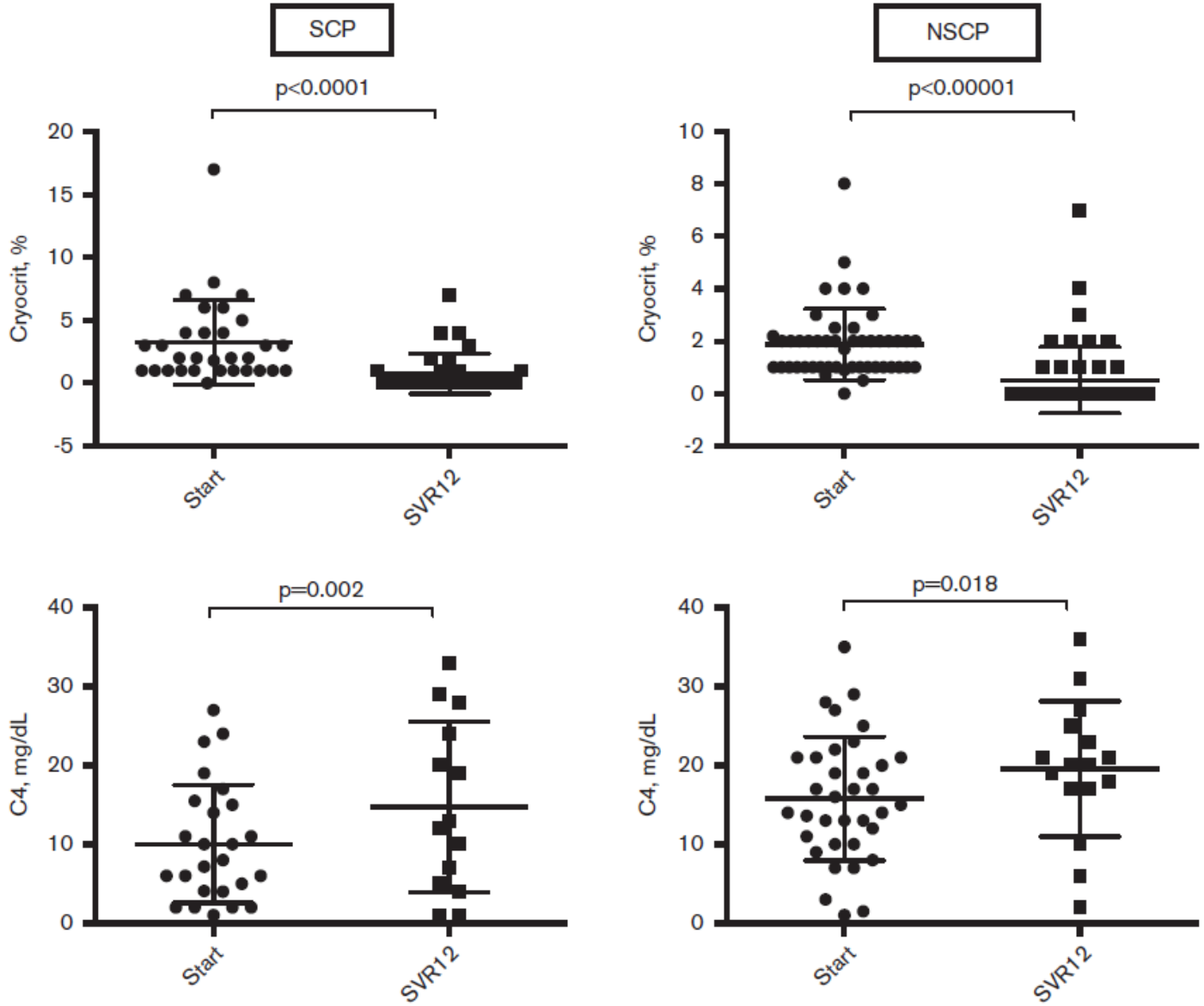
[a]Both the patients were treated with SOF + RBV (see Results section).

[b]The patient stopped the treatment because of severe nausea and vomiting.

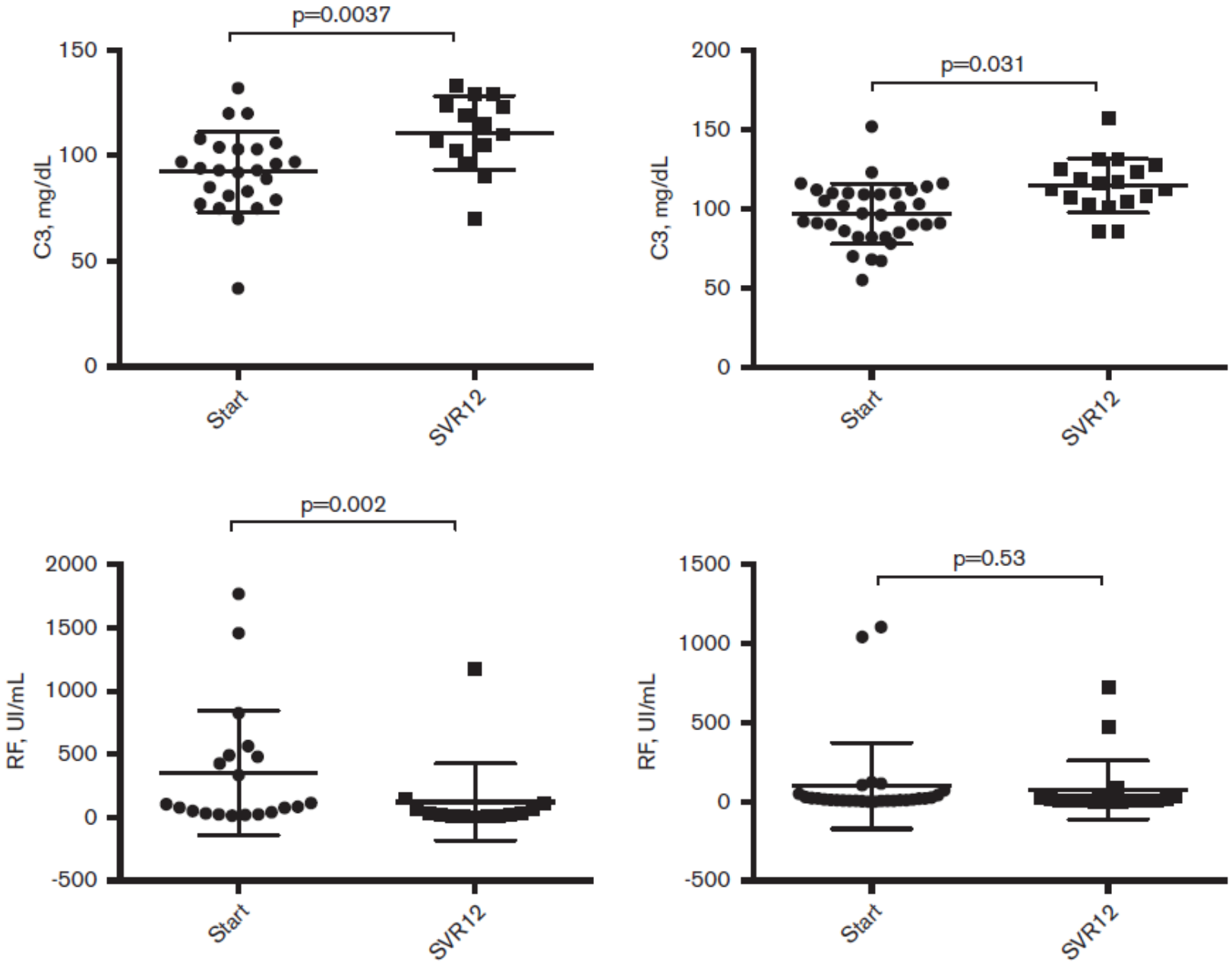
[c]Overdose.

[d]Cholangiocarcinoma.

Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215



Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215



Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215

Table 4. Differences in symptomatic cryoglobulinemic patient clinically responsive (completely or partially) and nonresponsive after direct-acting antivirals at sustained virological response 12

	Nonresponsive ($n=12$)	Responsive ($n=23$)	*P*-value
Age [mean (SD)]	71 (10.3)	65.61 (12.64)	0.22
Female [*n* (%)]	9 (75)	15 (65.1)	0.70
BMI [mean (SD)]	24 (2.5)	24 (3.35)	0.92
Cirrhosis [*n* (%)]	4 (33.3)	11 (47.82)	0.48
Fibroscan [median (IQR)]	7 (4.2–15.3)	8.0 (6.5–16.8)	0.14
Genotypes [*n* (%)]			
1	7 (58.3)	10 (43.5)	
2	4 (33.3)	8 (34.8)	
3	0 (0)	2 (8.7)	
4	1 (8.3)	3 (13)	
HCV-RNA [median (IQR)] (UI/ml)	151 287 (54 442–1 002 827)	436 146.5 (55 619.5–655 189)	0.33
ALT [median (IQR)]	32.5 (21.2–64.7)	47 (34.5–88)	0.45
Cryocrit [mean (SD)]	4 (5.15)	2.5 (1–4)	0.66
C3 [median (IQR)] (mg/dl)	93.5 (78.5–101.5)	93 (83–103.5)	0.97
C4 [median (IQR)] (mg/dl)	8 (4.5–14)	8 (4.5–14.7)	0.93
RF [median (IQR)] (UI/ml)	268 (72–569)	80 (40.7–375.7)	0.44
Symptoms [*n* (%)]			
Dermatologic	5 (41.6)	16 (69.5)	
Neurologic	7 (58.3)	6 (26)	
Muscoloskeletal	2 (16.6)	3 (13)	
Kidney	2 (16.6)	0	
LNH	1 (8.3)	0	
Immunological treatment [*n* (%)]			
Previous	5 (41.6)	3 (13)	
Current	2 (16.6)	1 (4.3)	
Previous + current	2 (16.6)	6 (26.1)	
No	3 (25)	13 (56.5)	

Among the 53 SCP, **the symptoms remained unchained in 12 (34.3%) despite SVR**, and regress completely in 15 (43%);

Among SCP, 11 patients without cryoglobulines at SVR12 still complained of cryoglobulines-related symptoms.

Passerini et al., Eur J Gastroenterol Hepatol.2018; 30(10):1208-1215

Direct-Acting Antivirals (DAAs) treatment Improves Hepatitis C Virus (HCV)-Associated Mixed Cryoglobulinemia Symptoms

Pollastri E[1], Spinetti A[1], Odolini S[1], Tomasoni L[1], Lanza P[1], Bonito A[1], Zaltron S[1], Nasta P[1], Urbinati L[1], Biasi L[1], Festa E[1], Casari S[1], Affatato S[2], Belotti E[2], Zani R[2], Scaini P[2], Cancarini G[2], Castelli F[1].

1. University Department of Infectious and Tropical Diseases, University of Brescia and Brescia Spedali Civili General Hospital, Brescia, Italy
2. University Department of Nephrology, University of Brescia and Brescia Spedali Civili General Hospital, Brescia, Italy

ABSTRACT

Mixed cryoglobulinemia (MC) is an extra-hepatic complication of HCV infection and virus clearance could lead to a remission of symptoms. We retrospectively analyzed data of HCV infected patients with MC who received DAAs treatment at our University Division of Infectious and Tropical Diseases of Spedali Civili, Brescia from March 2015 to October 2016. All patient achieved sustained virological response 24 weeks after end of treatment (SVR24). At SVR24 there was an improvement in neuropathy, purpura and cryocrit ($p<0.05$) with statistically significant difference to baseline.

OBJECTIVES

HCV is responsible of lymphoproliferative disorders such as mixed cryoglobulinemia (MC), which is characterized by multi-organ vasculitis. HCV clearance is related to remission of MC. This was observed also after dual-therapy-pegylated interferon (PEG-IFN) and ribavirin (RBV) but rates of HCV clearance were relatively low. Therapy with DAAs attains 90-95% of sustained virologic response (SVR; undetectable viral load at week 12 or 24 after end of treatment) and could lead to a long term response of MC. This study aims to evaluate efficacy of DAAs therapy on HCV-associated MC symptoms.

METHODS

We retrospectively analyzed data of HCV infected patients with MC who received DAAs treatment at our University Division of Infectious and Tropical Diseases of Spedali Civili, Brescia, from March 2015 to October 2016. SVR was assessed with HCV RNA levels under detection limit (<15 UI/mL) at 24 weeks after end of treatment (SVR24). Univariate analysis was used to compare clinical and biochemical response to treatment.

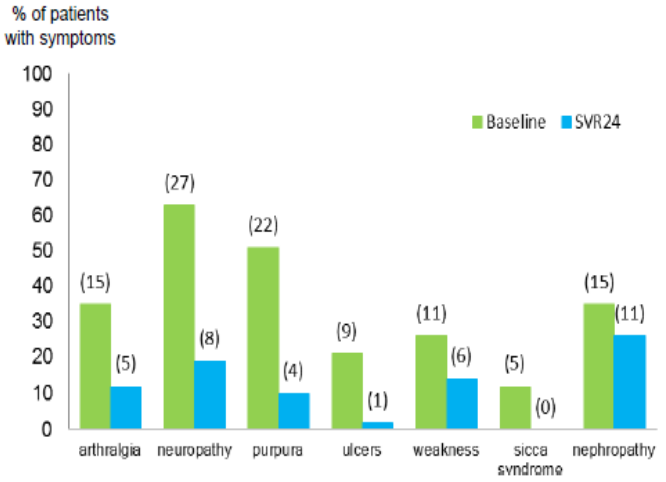
RESULTS

A total of 43 patients were analyzed, 32 females (74%) and 11 males (26%), with a mean age of 65-years-old. Genotype 1b was the prevalent HCV genotype (56%), followed by genotype 2 (19%), 1a (14%), 3 (5%) and 4 (5%). Liver fibrosis was calculated with FibroScan: mean stiffness was 7,5 KPa and 5 patients had a stiffness ≥ 13 KPa (mean score: 15.4 Kpa). Patients non responder to previous PEG-INF treatment were 13 (30%), those treated with immunosuppressive therapy before DAA were 28 (65%) and 7 (16%) patients had lymphoma. Favourite treatment regimens were sofosbuvir/simeprevir+RBV (23%) and sofosbuvir/ledipasvir±RBV (23%). Mean pre-treatment HCV RNA levels were 1,531,085 UI/ml and all patients achieved SVR24. Symptoms at baseline were arthralgia in 15 patients (35%), neuropathy in 27 (63%), purpura in 22 (51%), ulcers in 9 (21%), weakness in 11 (26%), sicca syndrome in 5 (12%) and nephropathy (nephritic, nephrotic, mixed syndrome or CrCl<60 ml/min) in 15 (35%) patients. Arthralgia, neuropathy, purpura, ulcers, weakness and nephropathy were observed respectively in 5 (12%), 8 (19%), 4 (10%), 1 (2%), 6 (14%) and 11 (26%) patients, with statistically significant difference to baseline for neuropathy and purpura ($p<0.05$). None had sicca syndrome. Mean cryocrit was 4.1% at baseline and 1.4% at SVR24 ($p<0.05$).

CONCLUSIONS

Our study confirms efficacy of DAAs treatment in achieving SVR24 in patients with MC and this is associated with a statistically significant improvement in clinical and biochemical manifestations of MC. Further follow-up will be required to determine if clinical improvement continues after viral clearance.

DAA REGIMEN	% patients (n.)
Sofosbuvir + Simeprevir	23,3% (10)
Sofosbuvir + Daclatasvir	11,6 % (5)
Sofosbuvir + Ledipasvir	23,3% (10)
Sofosbuvir	18,6% (8)
Dasabuvir + Ombitasvir + Paritaprevir + Ritonavir	18,6% (8)
Ombitasvir + Paritaprevir + Ritonavir	4,6% (2)
Ribavirin	37,2% (16)



N.B. In the brackets: number of patients with symptoms.

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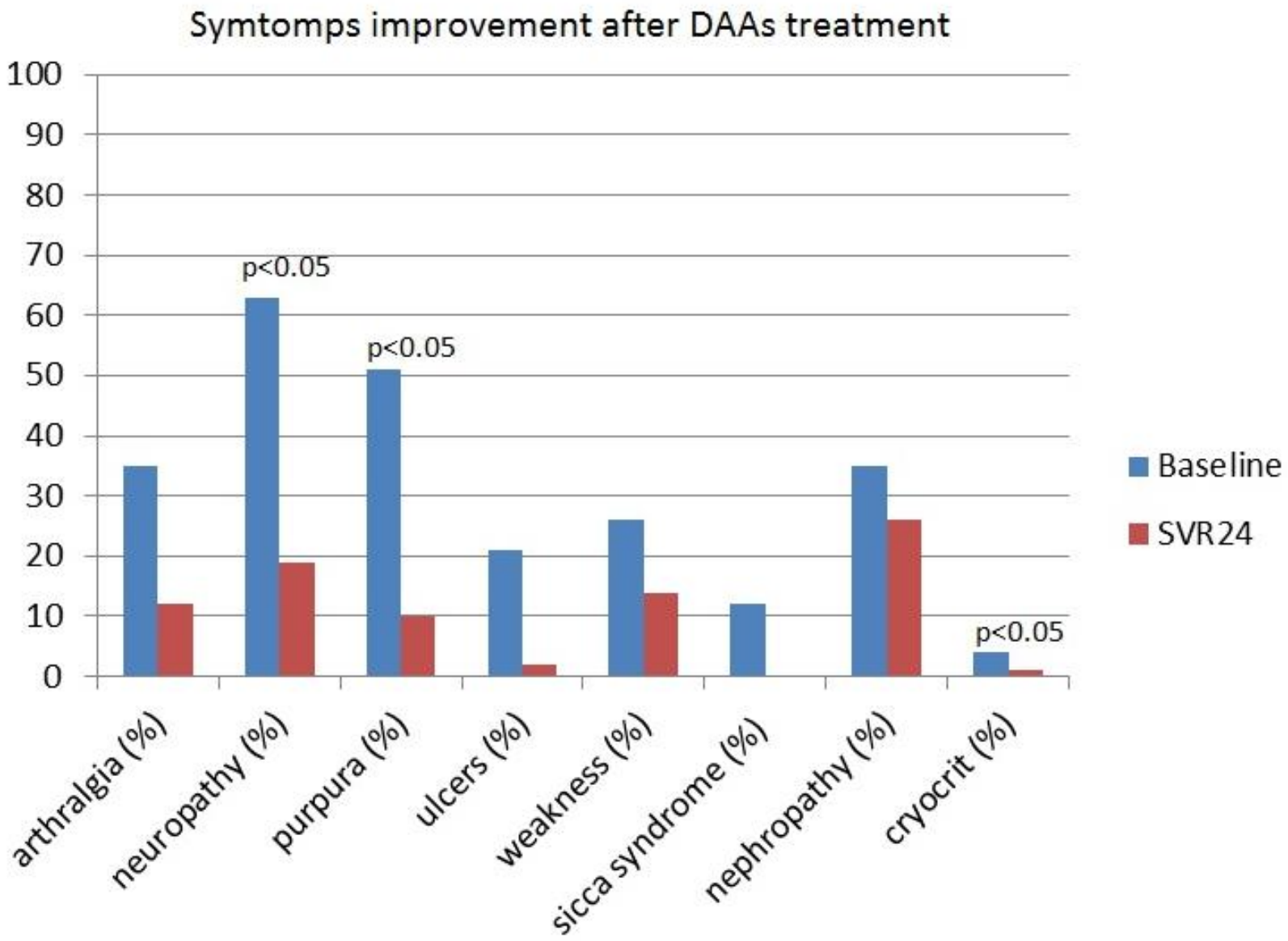
- 43 patients analyzed [32 females (74%) and 11 males (26%)];
- Mean age of 65 years old;
- Genotype 1b (56%), genotype 2 (19%), 1a (14%), 3(5%), 4(5%);
- Liver fibrosis: mean stiffness 7,5 KPa and 5 patients had a stiffness ≥ 13 Kpa (mean score 15,4 Kpa).



Miglioramento clinico nell'intera popolazione indagata significativo e duraturo soprattutto per porpora ed ulcere

Trend alla persistenza/rebound di alcune manifestazioni (neuropatia, artralgie, s. sicca)

5 casi di
flare renali post DAA
(1 caso "de novo")
Terapia IS
1 decesso

Oncotarget
Advance Online Publications

The challenge of treating hepatitis C virus-associated cryoglobulinemic vasculitis in the era of anti-CD20 monoclonal antibodies and direct antiviral agents

Roccatello D et al. Oncotarget 2017

THE POSSIBLE PERSISTENCE OF MC STIGMATA IN SPITE OF VIRAL ERADICATION:
INSUFFICIENT OR TOO LATE ANTIVIRAL TREATMENT ?

Zignego AL et al. Hepatology 2016

✓absence of immunomodulatory effects of DAA vs IFN

✓short follow-ups and a Kuppfer cell impairment in clearing IC

✓rebound effect of removal of IS therapies during DAA

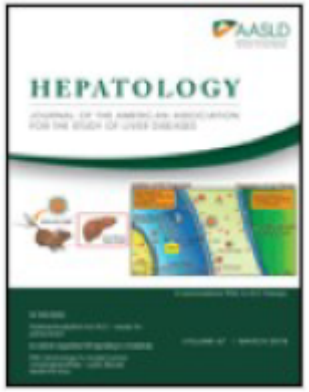
✓presence of irreversible damage (e.g. neurological, axonal)

✓no return points -> B-cell clonal expansion indipendent from the tiggering virus

Oncotarget
Advance Online Publications

The challenge of treating hepatitis C virus-associated cryoglobulinemic vasculitis in the era of anti-CD20 monoclonal antibodies and direct antiviral agents

Roccatello D et al. Oncotarget 2017



THE POSSIBLE PERSISTENCE OF MC STIGMATA IN SPITE OF VIRAL ERADICATION:
INSUFFICIENT OR TOO LATE ANTIVIRAL TREATMENT ?

Zignego AL et al. Hepatology 2016

La reversibilità della MC è inversamente correlata al grado del disordine linfoproliferativo e del danno d'organo

NECESSARIO ERADICARE PRECOCEMENTE L'INFEZIONE DA HCV

Outline of presentation

- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
- Insulin resistance
- Neurocognitive disorders

LYMPHOMA

- HVC infection is associated with B-cell NHL (observed during the course of MC or idiopathic)
- >35 - fold increased NHL risk in MC pts
- South-north gradient in the prevalence of HCV-associated NHL with some discrepancies (NHL attributable to HCV 10% in countries with high prevalence vs <1% in countries with low prevalence)

Ferri et al. JAMA 1994, Brit J Haematol 1994
Monti el al. Arch Intern Med 2005
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Dal Maso. Cancer Epidemic Biomarkers Prev 2006

MD Anderson Cancer Center
Making Cancer History®

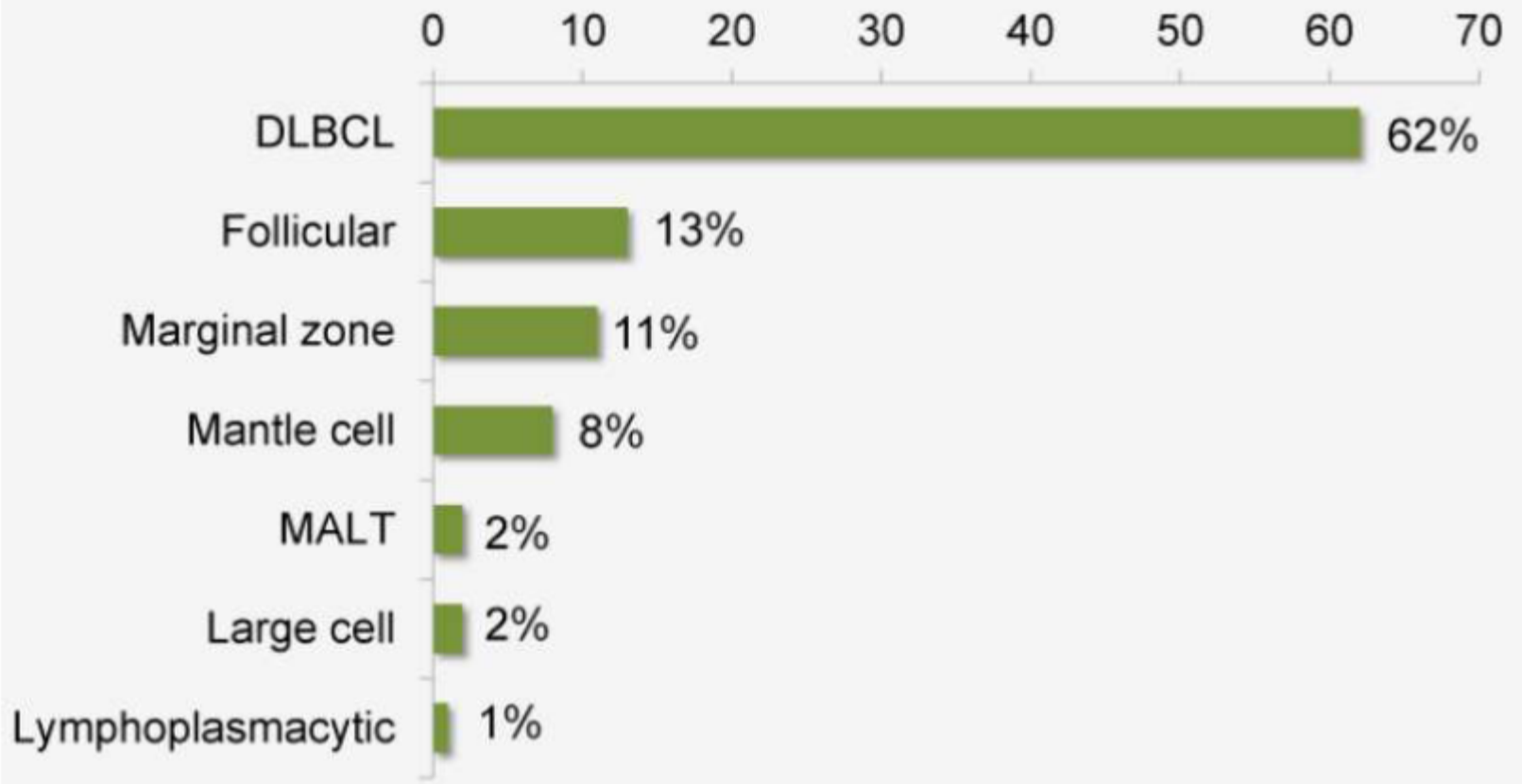
Poster # 1499

Most patients with hepatitis C virus (HCV)-associated lymphoma present with mild liver disease at cancer diagnosis: A call to revise indications for HCV treatment

Harrys A. Torres, MD, FACP; Parag Mahale, MBBS, MPH

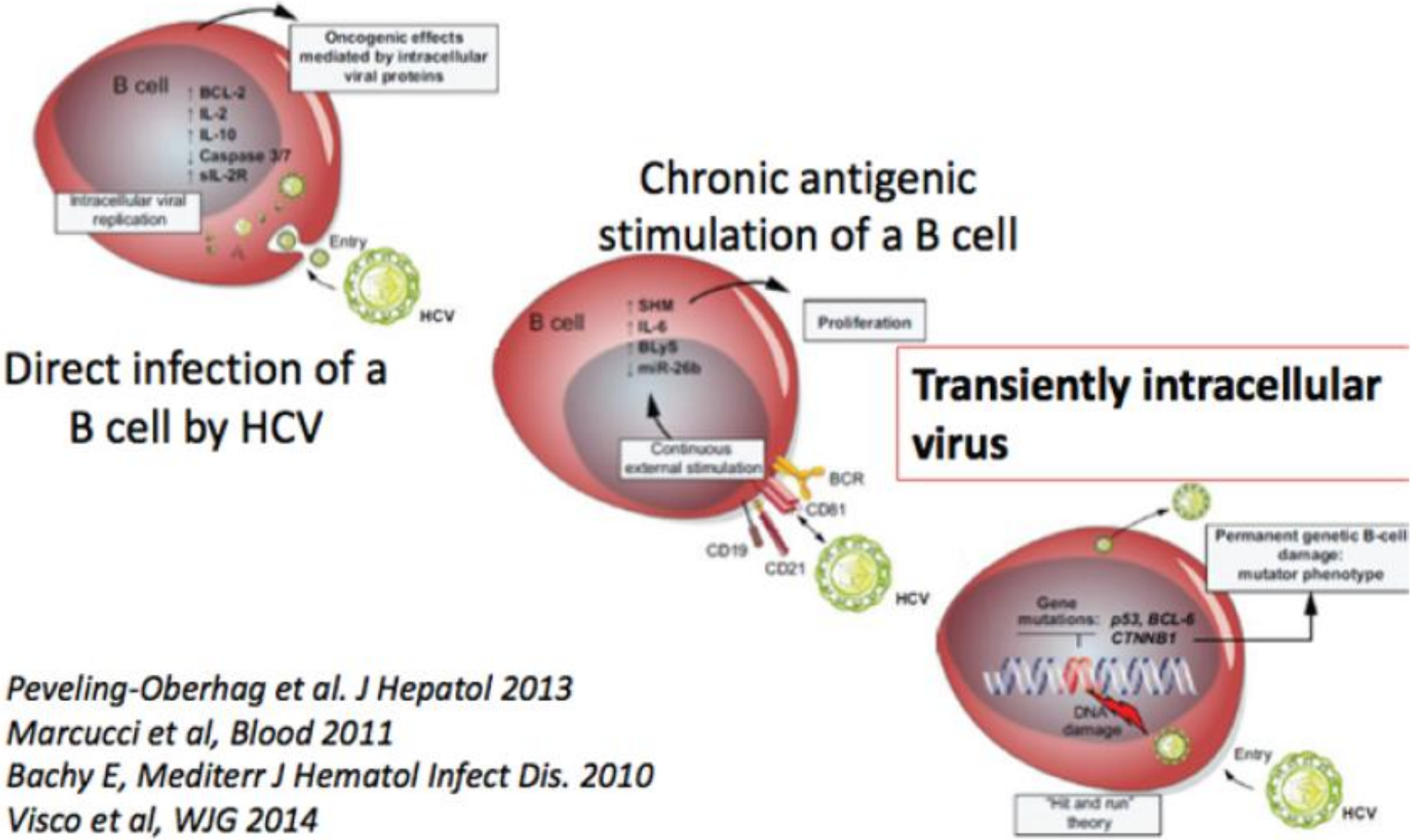
Department of Infectious Diseases, Infection Control & Employee Health, The University of Texas MD Anderson Cancer Center

Figure 1: Types of HCV-associated B-cell NHL



DLBCL: Diffuse large B cell lymphoma, MALT: Mucosa associated lymphoid tissue

HCV associated NHL pathogenesis



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Received: 21 November 2018 | Revised: 12 March 2019 | Accepted: 5 April 2019

DOI: 10.1111/liv.14119

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: A systematic review and meta-analysis

Mario Masarone | Marcello Persico

Key points

- HCV infection can now be treated easily also in "difficult patients" with direct antiviral agents.
- It has been associated to increased risk of malignancies, also non-hepatic.
- The present study evaluates the association between non-hepatic malignancies and HCV, and the effects of viral eradication on the oncological diseases.

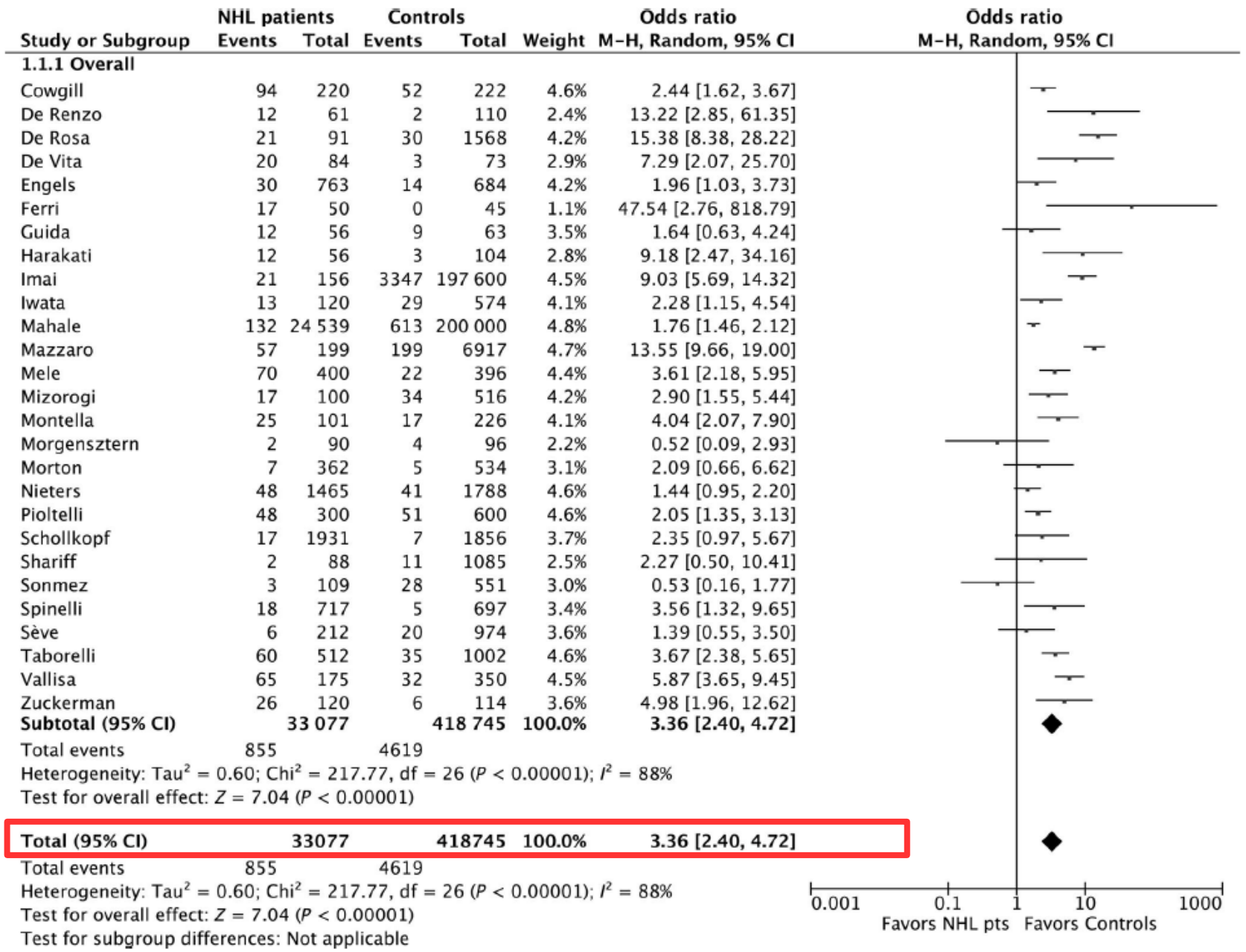
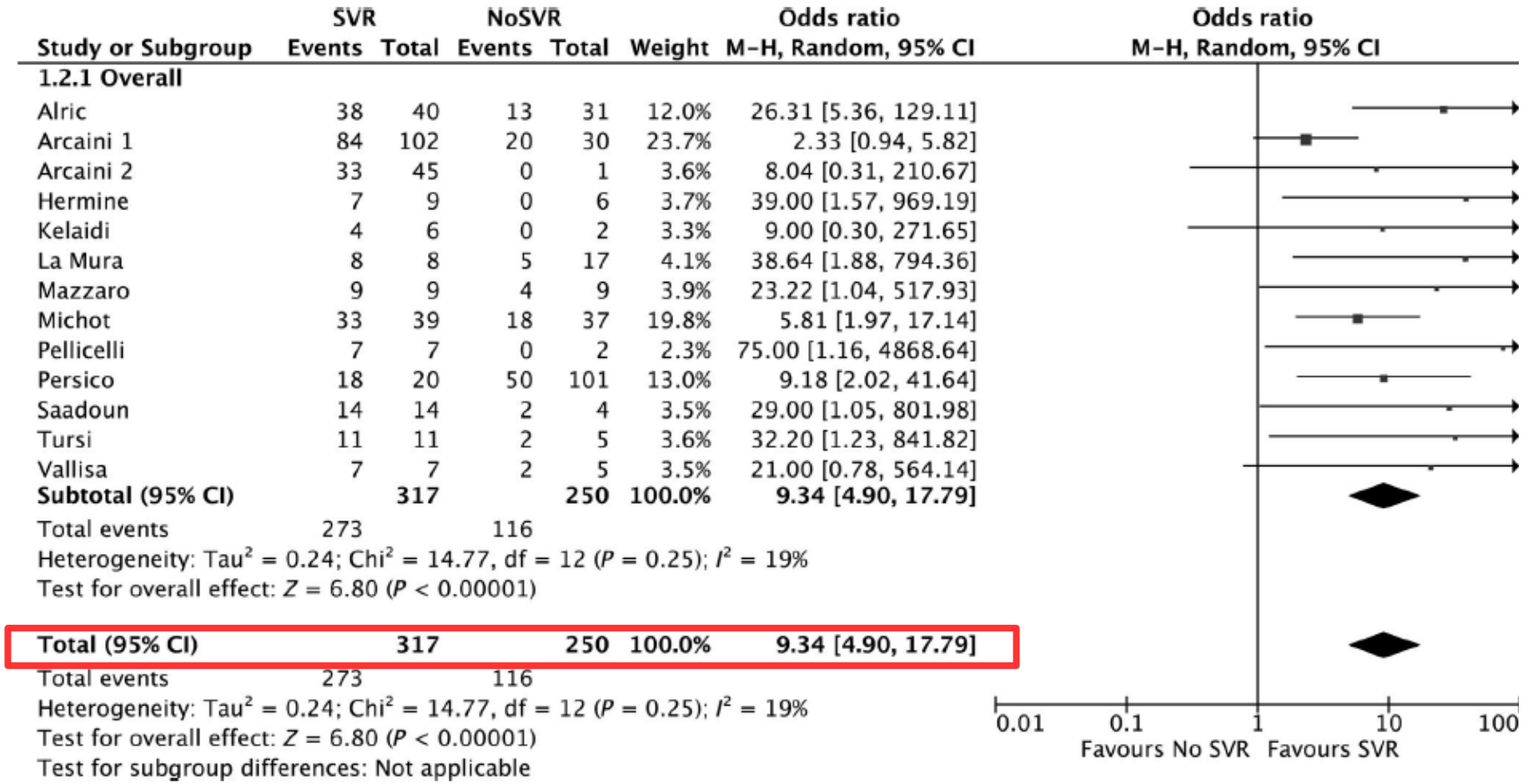


FIGURE 1 Forest plot of hepatitis C virus (HCV) prevalence in NHL patients. Random effect model. The metanalysis included 27 studies with a total of 33 077 NHL patients and 418 745 controls

HCV and NHL association:

- 27 studies with a total of 33077 NHL patients and 418 745 controls
- Global OR for the association between the prevalence of HCV infection and B-cell NHL was 3.36 (95% CI 2,40 – 4,71)



Study or Subgroup	SVR Events	SVR Total	NoSVR Events	NoSVR Total	Weight	Odds ratio M-H, Random, 95% CI
1.2.1 Overall						
Alric	38	40	13	31	12.0%	26.31 [5.36, 129.11]
Arcaini 1	84	102	20	30	23.7%	2.33 [0.94, 5.82]
Arcaini 2	33	45	0	1	3.6%	8.04 [0.31, 210.67]
Hermine	7	9	0	6	3.7%	39.00 [1.57, 969.19]
Kelaidi	4	6	0	2	3.3%	9.00 [0.30, 271.65]
La Mura	8	8	5	17	4.1%	38.64 [1.88, 794.36]
Mazzaro	9	9	4	9	3.9%	23.22 [1.04, 517.93]
Michot	33	39	18	37	19.8%	5.81 [1.97, 17.14]
Pellicelli	7	7	0	2	2.3%	75.00 [1.16, 4868.64]
Persico	18	20	50	101	13.0%	9.18 [2.02, 41.64]
Saadoun	14	14	2	4	3.5%	29.00 [1.05, 801.98]
Tursi	11	11	2	5	3.6%	32.20 [1.23, 841.82]
Vallisa	7	7	2	5	3.5%	21.00 [0.78, 564.14]
Subtotal (95% CI)		**317**		**250**	**100.0%**	**9.34 [4.90, 17.79]**
Total events	273		116			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 14.77$, df = 12 ($P = 0.25$); $I^2 = 19\%$
Test for overall effect: $Z = 6.80$ ($P < 0.00001$)

Total (95% CI)		**317**		**250**	**100.0%**	**9.34 [4.90, 17.79]**
Total events	273		116			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 14.77$, df = 12 ($P = 0.25$); $I^2 = 19\%$
Test for overall effect: $Z = 6.80$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

FIGURE 2 Forest Plot of Response to antiviral therapy in HCV infected NHL patients on NHL survival (Progression free survival). Random effect model. The metanalysis included 13 studies with a total of 273 HCV patients with NHL who achieved SVR with AT and 250 who did not achieve SVR (No-SVR) or did not perform AT therapy at all

SVR and NHL outcome:

- 13 studies for a total of 317 patients and 250 controls;
- 9 studies conducted in the IFN era and 4 in the DAA era;
- Patients with an SVR had a pooled OR for a better NHL outcome (in terms of progression free survival) with respect to controls, namely OR 9,34 (95% CI 4.9 – 17.79).

New Microbiologica, 41, 3, 242-245, 2018, ISSN 1121-7138

CASE REPORT

Feasibility of all-oral anti-HCV treatment during DHAP chemotherapy and autologous stem cell transplantation for T-cell lymphoma

Roberto Rossotti[1], Chiara Rusconi[2], Chiara Baiguera[1], Vittorio Ruggero Zilioli[2], Giovanni Grillo[2], Marco Merli[1], Emanuele Ravano[2], Massimo Puoti[1]

[1]Niguarda Hepatitis Center, Division of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;
[2]Niguarda Cancer Center, Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

SUMMARY

The role of anti-HCV direct-acting agents (DAAs) is well described in HCV-related lymphoproliferative disorders, whereas few data are available on their use in other malignancies, such as aggressive T-cell lymphomas requiring autologous stem cell transplantation (ASCT). We describe two oncologic cirrhotic patients treated with DAAs who underwent ASCT achieving cure for both diseases. Co-administration of sofosbuvir with cisplatin led an unexpected severe kidney impairment that did not resolve 30 weeks after drug exposure. The optimal timing of DAA administration in the ASCT setting has yet to be defined: our experience shows that co-administration is feasible, but requires close monitoring for adverse events.

Table 1. *Clinical features of hematologic patients treated with DAA so far published.*

Author	*N*	*Histology*	*DAA regimen*	*Chemotherapy regimen*	*Timing of DAA*	*Toxicity*	*SVR*	*Complete response*
Carrier	5	Marginal zone lymphoma (2)	SOF+SMV	Rituximab	During rituximab infusion	G3 asthenia	100% (5/5)	100% (5/5)
		Marginal zone lymphoma (1)	SOF+DCV			No		
		DLBCL (2)	SOF+DCV	4 R-ACVBP, 2 Methotrexate, 4 R-VP16	After CT	G3 liver toxicity		
Merli	2	DLBCL (1)	SOF+SMV	R-CHOP, R-mini-DHAP followed by RT	After CT, during RT	No	100% (2/2)	100% (2/2)
		DLBCL (1)	SOF/LDV	R-CHOP	Contemporary			
Economides	9	Multiple myeloma (2);	SOF/LDV±RBV (52%) SOF+RBV (29%) SOF+SMV (14%) SOF+DCV (5%)*	No detailed data	Contemporary	Serious adverse events: 38% (8/21): G3: Anemia Neutropenia Thrombocytopenia Fatigue Weight loss Headache G4: Abdominal pain Fatigue	95% (20/21)*	No data
		Myelodysplastic syndrome (2)						
		Acute myelogenous leukemia (1)						
		DLBCL (1)						
		Follicular lymphoma (1)						
		Waldenström macroglobulinemia (1)						
		Mycosis fungoides/T cell lymphoma (1)						
Kyvernitakis	14	Leukemia (14); Non-Hodgkin lymphoma (20); Hodgkin lymphoma (9); Multiple myeloma (25); other (1)*	SOF+RBV (6)	No detailed data	After HSCT	G3 anemia	85% (11/13)	32/64 (50%)*
			SOF+SMV (2)			No		
			SOF/LDV±RBV (6)			G3 hyperbilirubinemia		
Total	30					29% (12/42)*	90% (18/20)**	55% (39/71)^

* Including the full study population; ** excluding patients described by Economides for whom no distinction between oncologic and hematologic subjects is available; ^: including the full population described by Kyvernitakis and excluding the subjects described by Economides.
SMV: simeprevir; LDV: ledipasvir; DLBCL: Diffuse Large B-cell Lymphoma; R-ACVBP: rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin and cytarabine; R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone; CT: chemotherapy; RT: radiotherapy; G3/G4: grade 3/grade 4 toxicity according to Common Terminology Criteria for Adverse Events, CTCAE, version 4.03 published in 2010).

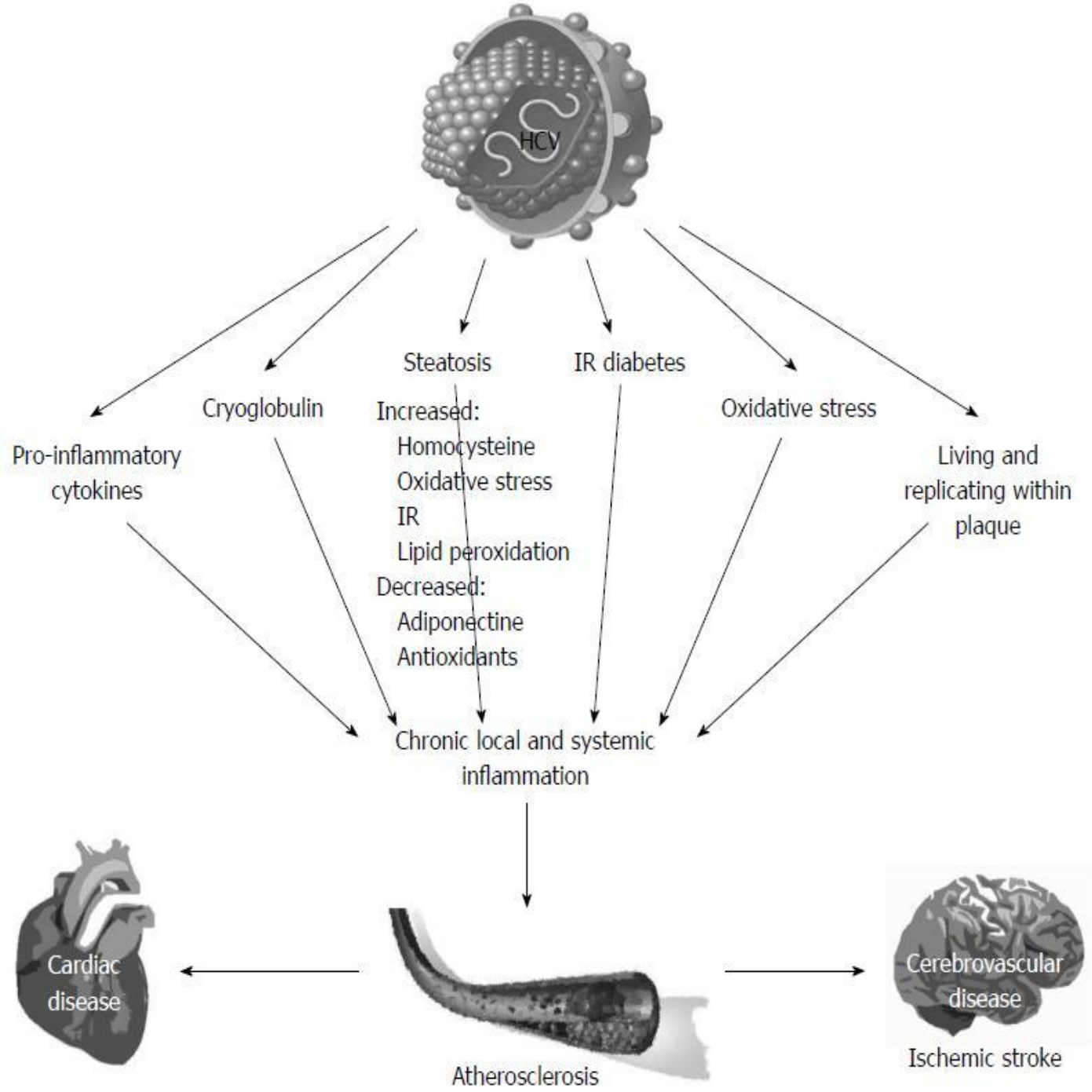
Outline of presentation

- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
- Insulin resistance
- Neurocognitive disorders

ATHEROSCLEROSIS AND CARDIOVASCULAR DISEASE

Direct and Indirect HCV pro-atherogenic mechanism:

- HCV lives and replicates within carotid plaques promoting a local enviroment of pro-athoregenic factors;
- HCV causes conditions such as insulin resistance, diabetes, hepatic steatosis, cryoglobulineamia that are associated with development of atherosclerosis and cardiovascular disease

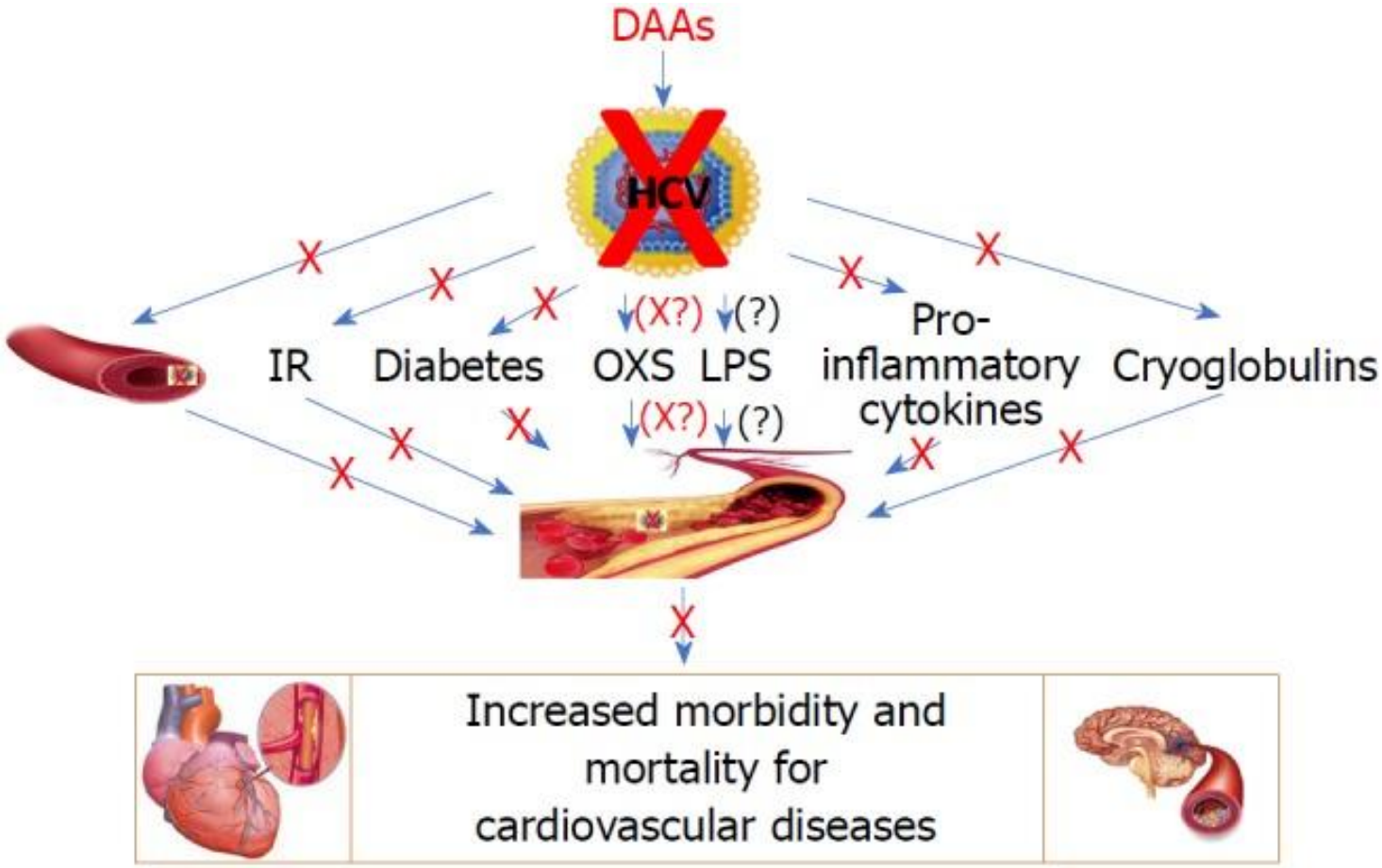


HCV infected patients had higher risk of death for cardiovascular events compared to controls (HR 1.50, CI 1.10-2.03)

Lee et al., 2012

Cacoub et al., Ther Adv Infect Dis 2016

Can eradication of HCV improve atherosclerosis and reduce the risk of cardiovascular disease?



Adinolfi et al, World J Gastroenterl 2018; November 7; 24(41): 4617-4621

J Hepatol. 2018 Jul;69(1):18-24. doi: 10.1016/j.jhep.2018.02.015. Epub 2018 Mar 2.

Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis.

Petta S[1], Adinolfi LE[2], Fracanzani AL[3], Rini F[4], Caldarella R[5], Calvaruso V[4], Cammà C[4], Ciaccio M[5], Di Marco V[4], Grimaudo S[4], Licata A[4], Marrone A[2], Nevola R[2], Pipitone RM[4], Pinto A[6], Rinaldi L[2], Torres D[6], Tuttolomondo A[6], Valenti L[3], Fargion S[3], Craxì A[4].

- Multicenter Italian Study of 182 patients treated with DAA with F3 fibrosis or compensated cirrhosis (66%);
- Carotid atherosclerosis evalutaed at BL, and 9-12 months after treatment;
- 56% male, mean age 63 years, 14% obesity, 42% hypertension, 20% DM;
- At the end of follow up a significant decrease in mean carotid thickness was observed, without effect of carotid plaques;
- No changes in BMI, significant increase in cholesterol levels;

- IN PATIENTS WITH ADVANCED ATHEROSCLEROSIS, HCV ERADICATION DID NOT LEAD TO SIGNIFICANT CHANGES IN CAROTID PLAQUE.

Outline of presentation

- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
- Insulin resistance
- Neurocognitive disorders

INSULIN RESISTANCE AND DIABETES MELLITUS

- HCV infection is associated with a higher prevalence of type 2 diabetes mellitus ;
- Adults aged > 40 years with HCV were 4 times more likely to have concurrent diabetes thant those without HCV;
- Antonelli et al studied 564 noncirrhotic HCV infected patients control-matched with noncirrhotic HBV infected patients → increased prevalence rate of T2DM of 12% versus 4.9% in controls (p = 0.008)

Hum J et al, Clin Liver Dis 2018, Apr 6, 11(3): 73-76
Antonelli et al., Diabetes Care 2005; 28:2548-2550

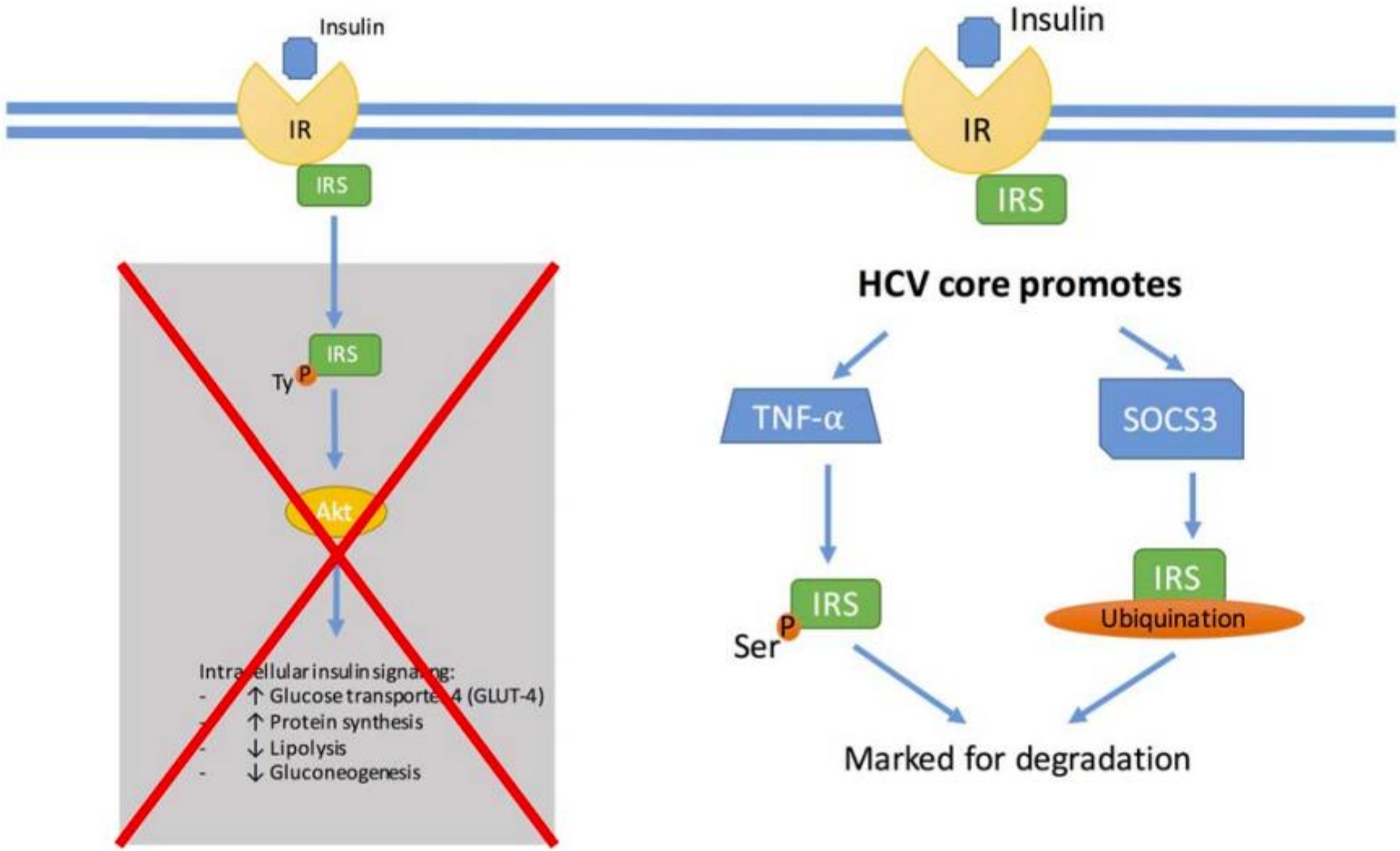


FIG 2 HCV leads to the upregulation of inflammatory cytokines such as TNF-α, which leads to serine phosphorylation of IRS and marks the protein for degradation. HCV core protein also promotes cytokine signaling 3 (SOCS3), causing ubiquitination of IRS and marking it for degradation. These mechanisms prevent the downstream effects of AKT activation, thus leading to insulin resistance.

Hum J et al, Clin Liver Dis 2018, Apr 6, 11(3): 73-76

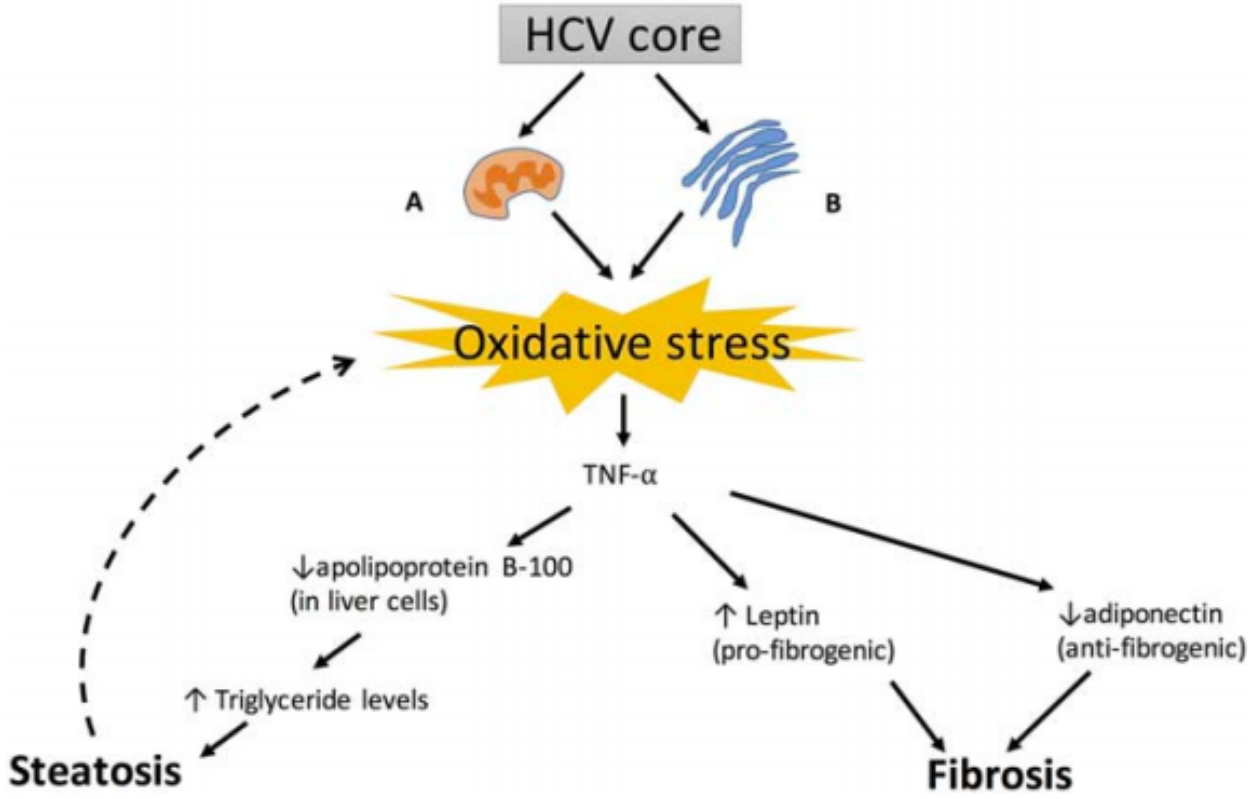


FIG 3 (A) At the mitochondria of hepatocytes, HCV core protein promotes intracellular calcium, which increases the reactive oxygen species (ROS) production through the electron transport chain. (B) At the ER of hepatocytes there is viral replication causing assembly chaperones to be overloaded, and misfolded proteins lead to ER dysfunction and increased ROS. The oxidative stress of HCV leads to triglyceride accumulation within hepatocytes by upregulating apolipoprotein B-100, causing a cycle of steatosis and more oxidative stress. Leptin is also upregulated and adiponectin downregulated, eventually leading to fibrosis of the liver.

- HCV core protein leads to oxidative stress by causing dysfunction at the mitocondria and endoplasmic reticulum (ER) of hepatocytes.

The oxidative stress increase s inflammatory cytokines such as TNF-alfa → hypernsulinemia, decresease apolipoprotein B-100, enhance TG accumulation in the liver and leads to steatosis –> more oxidative stress → increase leptin (profibrogenetic factor) → fibrosis

Hum J et al, Clin Liver Dis 2018, Apr 6, 11(3): 73-76

Eur J Gastroenterol Hepatol. 2019 Jan;31(1):16-23. doi: 10.1097/MEG.0000000000001215.

Insulin resistance does not impair response of chronic hepatitis C virus to direct-acting antivirals, and improves with the treatment.

Elhelbawy M[1], Abdel-Razek W, Alsebaey A, Hashim M, Elshenawy H, Waked I.

- There is a close relationship between HCV and diabetes mellitus, where the prevalence of HCV is higher in patients with diabetes mellitus [10] and patients with HCV-related liver disease also have a higher prevalence of diabetes mellitus.

- Insulin resistance (IR) is responsible for decreased response to PegIFN/RBV therapy, steatosis, liver fibrosis, and cirrhosis complications, especially varices and hepatocellular carcinoma.

THIS STUDY AIM TO ASSESS THE IMPACT OF DAAs THERAPY ON IR STATUS IN PATIENTS WITH CHRONIC HCV

Table 1. Baseline criteria of responders and nonresponders patients to hepatitis C virus direct-acting antivirals therapy

	HCV SVR status ($N = 511$)		
	Nonresponder [46 (9)]	SVR [465 (91)]	*P*
Age (years)	54.17 ± 8.44	50.28 ± 10.54	0.023
BMI (kg/m^2)	31.56 ± 5.53	29.85 ± 7.68	0.141
Total bilirubin (mg/dl)	1.1 ± 0.59	0.81 ± 0.41	0.001
Albumin (g/dl)	3.88 ± 0.48	4.05 ± 0.50	0.028
AST (U/l)	56.5 (35.25)	51 (43)	0.855
ALT (U/l)	46.5 (40.5)	52 (51.5)	0.065
Hemoglobin (g/l)	14.00 ± 1.85	14.56 ± 1.71	0.035
WBCs (×10^3/µl)	5.91 ± 1.95	6.51 ± 2.43	0.105
Platelets (×10^3/µl)	136.15 ± 61.40	171.15 ± 66.47	0.001
INR	1.14 ± 0.11	1.36 ± 5.42	0.783
Baseline HCV PCR (IU/l)	1 953 895.28 ± 2 920 375.56	1 374 046.61 ± 2 323 786.80	0.166
Liver stiffness score (kPa)	23.74 ± 15.22	18.37 ± 13.77	0.018
Sex			
Male	37 (80.4)	352 (75.7)	0.587
Female	9 (19.6)	113 (24.3)	
Diabetes mellitus			
No	32 (69.6)	353 (75.9)	0.370
Yes	14 (30.4)	112 (24.1)	
Treatment status			
Naive	29 (63)	330 (71)	0.310
Experienced	17 (37)	135 (29)	
Hypertension			
No	41 (89.1)	405 (87.1)	0.820
Yes	5 (10.9)	60 (12.9)	
Liver fibrosis			
Non-F4	16 (37.2)	255 (55.8)	0.024
F4	27 (62.8)	202 (44.2)	

Data were expressed as mean ± SD for parametric data, median (interquartile range) for nonparametric data, and number (percentage) for nominal data.
ALT, alanine aminotransferase; AST, aspartate transaminase; HCV, hepatitis C virus; INR, international normalized ratio; SVR, sustained virological response; WBC, white blood cells.

Table 2. Insulin resistance panel of responder and nonresponder patients to hepatitis C virus direct-acting antivirals therapy

	HCV SVR status ($N=511$)			
	Nonresponder [46 (9)]	SVR [465 (91)]	Total	*P*
Baseline (pretreatment) HOMA	3.66 (2.88)	3.21 (2.36)	3.24 (2.49)	0.098
12 weeks post-treatment HOMA	3.33 (2.47)	1.9 (1.58)	1.95 (1.61)	0.0001
Delta HOMA (post−pre)	−0.07 (2.57)	−1.09 (1.8)	−1.03 (1.89)	0.001
Baseline insulin resistance				
None	7 (15.2)	92 (19.8)	99 (19.4)	0.560
Yes	39 (84.8)	373 (80.2)	412 (80.6)	
12 weeks post-treatment insulin resistance				
None	9 (19.6)	260 (55.9)	269 (52.6)	0.0001
Yes	37 (80.4)	205 (44.1)	242 (47.4)	
12 weeks post-treatment insulin resistance course				
Persistent	34 (73.9)	196 (42.2)	230 (45)	0.001
Resolved	5 (10.9)	177 (38.1)	182 (35.6)	
Post-treatment de-novo IR	3 (6.5)	9 (1.9)	12 (2.3)	
None	4 (8.7)	83 (17.8)	87 (17)	

Data were expressed as median (interquartile range) for nonparametric data and as number (percentage) for nominal data.
HCV, hepatitis C virus; HOMA, homeostatic model assessment; SVR, sustained virological response.

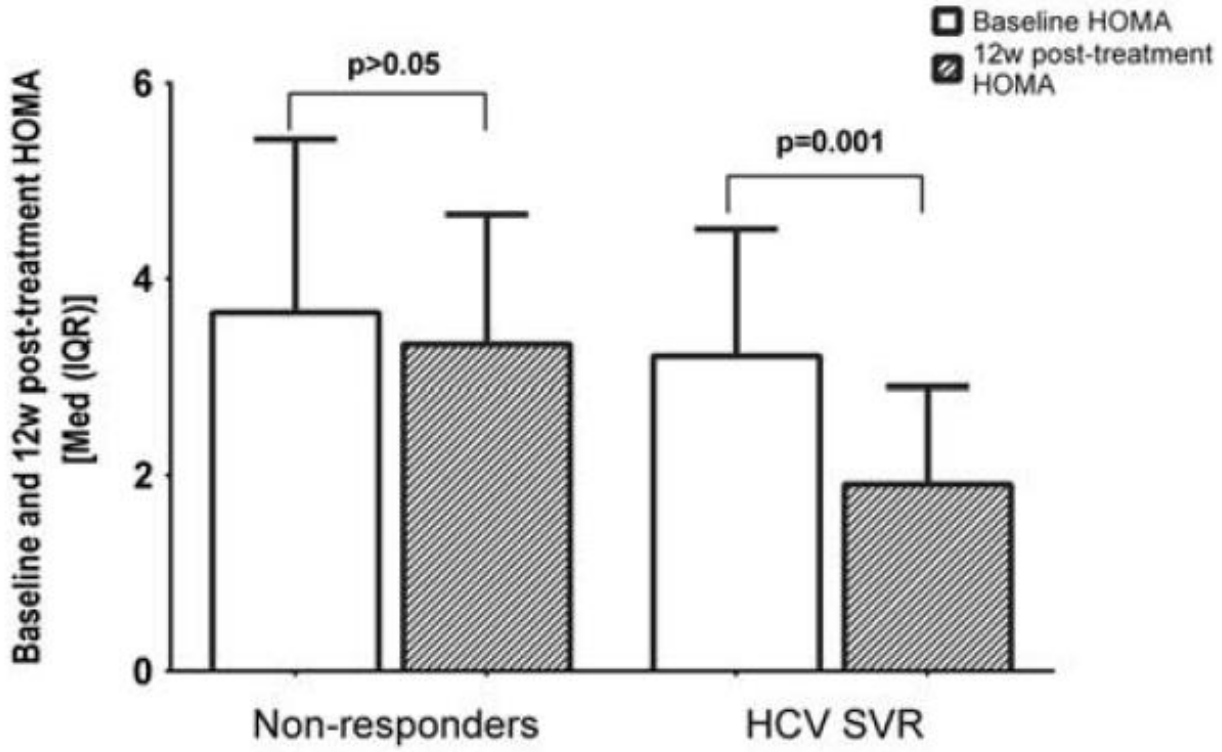
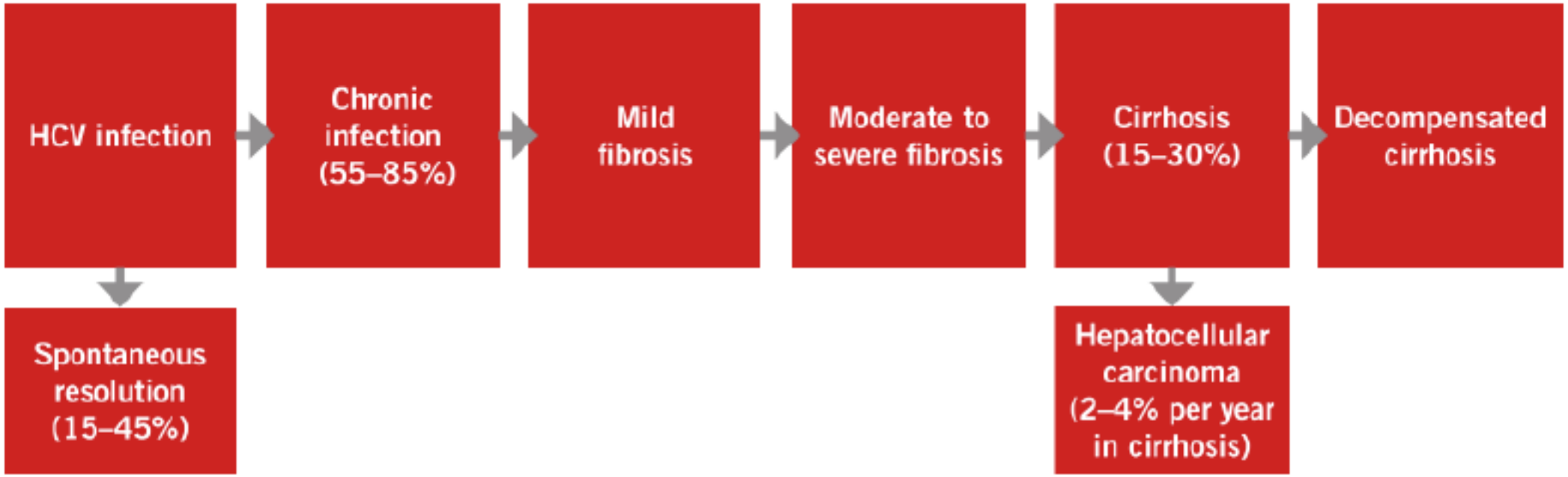


Fig. 1. Comparison of baseline insulin resistance 12 weeks post-treatment insulin resistance of responder and nonresponder patients to hepatitis C virus direct-acting antivirals therapy. HCV, hepatitis C virus; HOMA, homeostatic model assessment; IQR, interquartile range; SVR, sustained virological response.

Outline of presentation

- Cryoglobulinemic vasculitis
- Lymphoma and hematologic disorders
- Atherosclerosis and cardiovascular diseases
- Insulin resistance
- Neurocognitive disorders

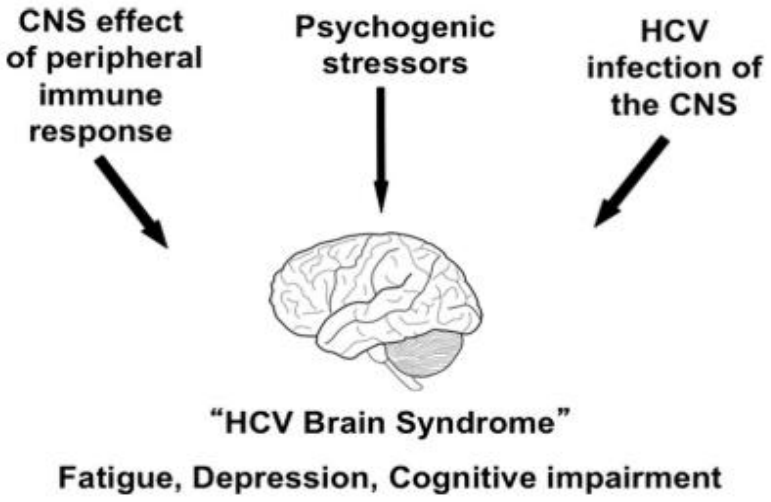
Natural History of Hepatits C: Asymptomatic in 90% of cases



Is it real?

***Patient Reported Outcomes* (PROs)**

- Qualità della vita
- Produttività lavorativa
- Fatica



Deficit cognitivo

Manifestazioni psichiatriche

(depressione)

- Circa il **50%** dei soggetti infetti riporta delle **alterazioni delle performance neurocognitive e dei disturbi neuropsichiatrici**;

- In particolare: problemi di concentrazione, di attenzione, della memoria di lavoro, di apprendimento, delle funzioni esecutive (ragionamento, capacità di astrazione, funzioni verbali, flessibilità mentale) e un generale rallentamento psicomotorio;

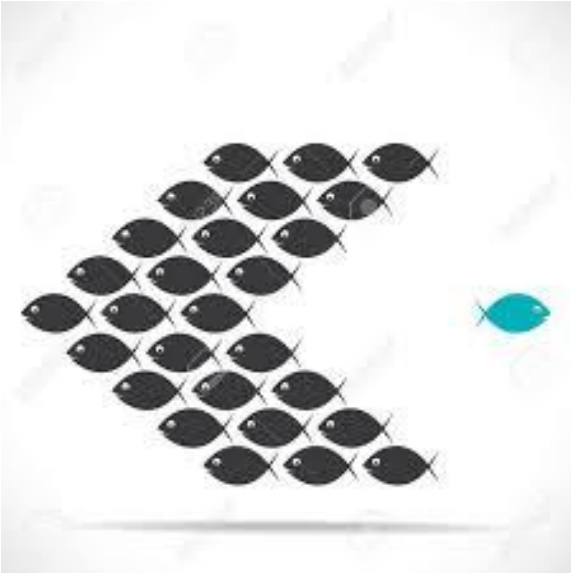
- Il 53-80% dei pazienti riporta una sensazione di **fatica**, intesa come un soggettiva mancanza di energia, esaurimento sia fisico che mentale, accompagnata dalla mancanza di motivazione e dalla difficoltà a iniziare e terminare un'azione;

- Circa 1/3 dei pazienti lamenta **episodi depressivi** e sono frequenti anche **ansia, insicurezza, aggressività, psicosi, insonnia.**

- Il 15% soffre di episodi ricorrenti di depressione. Il 60% soffre di insonnia e alterazioni ritmo circadiano.

Zampino et al., World J Hepatology, 2013
Monaco et al., World J Gastroenterolgy, 2015
Adinolfi et al.,World J Gastroenterolgy, 2015

QUESTO ACCADE INDIPENDENTEMENTE DAL GRADO DI FIBROSI EPATICA!



MINIMAL HEPATIC ENCEPHALOPATY (MHE)

- Alterazioni elettroencefalografiche e disturbi neuropsicologici (riduzione attenzione selettiva, delle abilità visuo-costruttive e delle funzioni motorie);
- Grave compromissione dell'attenzione e dello stato di coscienza (OVERT HE);
- Nell'MHE vi è una diffusa disintegrazione della sostanza bianca con danno corticale focale;
- Non è specifica dell'infezione da HCV ma può presentarsi in tutti i casi di insufficienza epatica.

Monaco et al., World J Gastroenterolgy, 2015
Solinas et al.,World J Hepatology, 2015

QUALI MECCANISMI SONO ALLA BASE DI QUESTI DISTURBI?

- Fattori predisponenti: età avanzata, **sesso femminile**, scarsa vita sociale;

- Impatto psicologico che la conoscenza stessa della malattia ha sul paziente: preoccupazione per terapia e prognosi, emarginazione sociale, stigma;

- Sottostante problema psichiatrico o altri disturbi che possono favorirne la comparsa o il peggioramento (Tossicodipendenza, abuso d'alcool).

Monaco et al., World J Gastroenterolgy, 2015
Adinolfi et al, World J Gastroenterolgy,2015
Yarlott et al.,J Advanced Research, 2016

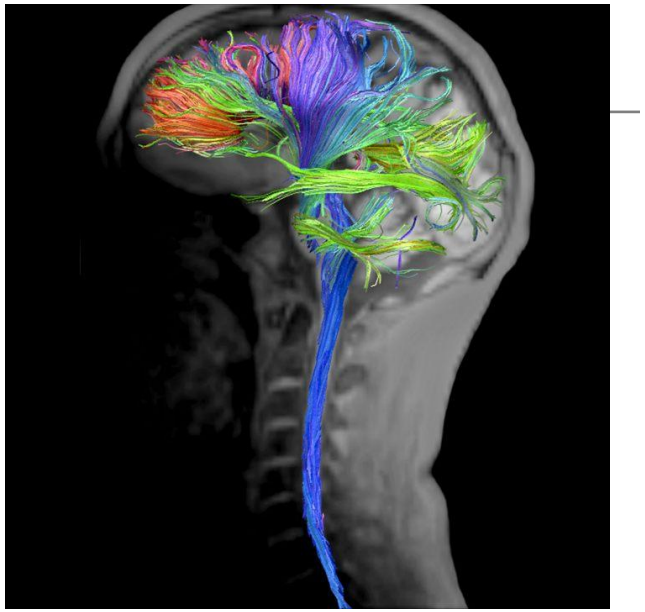
QUALI MECCANISMI SONO ALLA BASE DI QUESTI DISTURBI?

Invasione diretta del SNC da parte del virus HCV, soprattutto in presenza di alta carica virale circolante (ritrovati frammenti di genoma e proteine virali nel LCR);

- Sembra che l'HCV penetri l'encefalo infettando le cellule mononucleate plasmatiche (PBMC), che passano la Barriera Emato-Encefalica (BEE) (analogamente all'HIV);
- HCV può infettare le cellule endoteliali microvascolari encefaliche e ne induce l'apoptosi → alterazione permeabilità BEE che facilita ulteriormente il passaggio di virus e citochine infiammatorie circolanti → ulteriore alterazione permeabilità BEE.
- Attivazione e proliferazione della microglia e produzione di IL-8 e TNF-alfa → stimolazione risposta infiammatoria → danno neuronale;
- Stimolazione da parte della proteina del core di HCV della via di segnalazione ERK/STAT3→ morte neuronale, danno dendritico con astrogliosi, alterazioni citoscheletro neuronale.

Paulino et al, J NeuroVirology, 2012
Fletcher et al, Gastroenterology 2012
Adinolfi et al,World J Gastroenterolgy, 2015
Yarlott et al.,J Advanced Research, 2016

QUALI MECCANISMI SONO ALLA BASE DI QUESTI DISTURBI?



- Aumento del rapporto colina (markers sintesi membrana neuronale) e creatina a livello della sostanza bianche e gangli base;

→ NON PRESENTE IN HBV
→ rapporto diminuito in MHE

- Aumento del rapporto mioinositolo/creatina (marker infiammazione e gliosi);
- Aumento N-acetilaspartato (NAA) (indicativo di fenomeni di riparo e di neuroprotezione come compenso allo stato infiammatorio);
- Ipoperfusione dei gangli della base e della corteccia cerebrale;
- Diminuzione del metabolismo del glucosio aree limbiche, corteccia frontale, parietale e corticale;
- Alterazione della trasmissione dopaminergica e serotoninergica a livello mesencefalico e nel settore striatale.

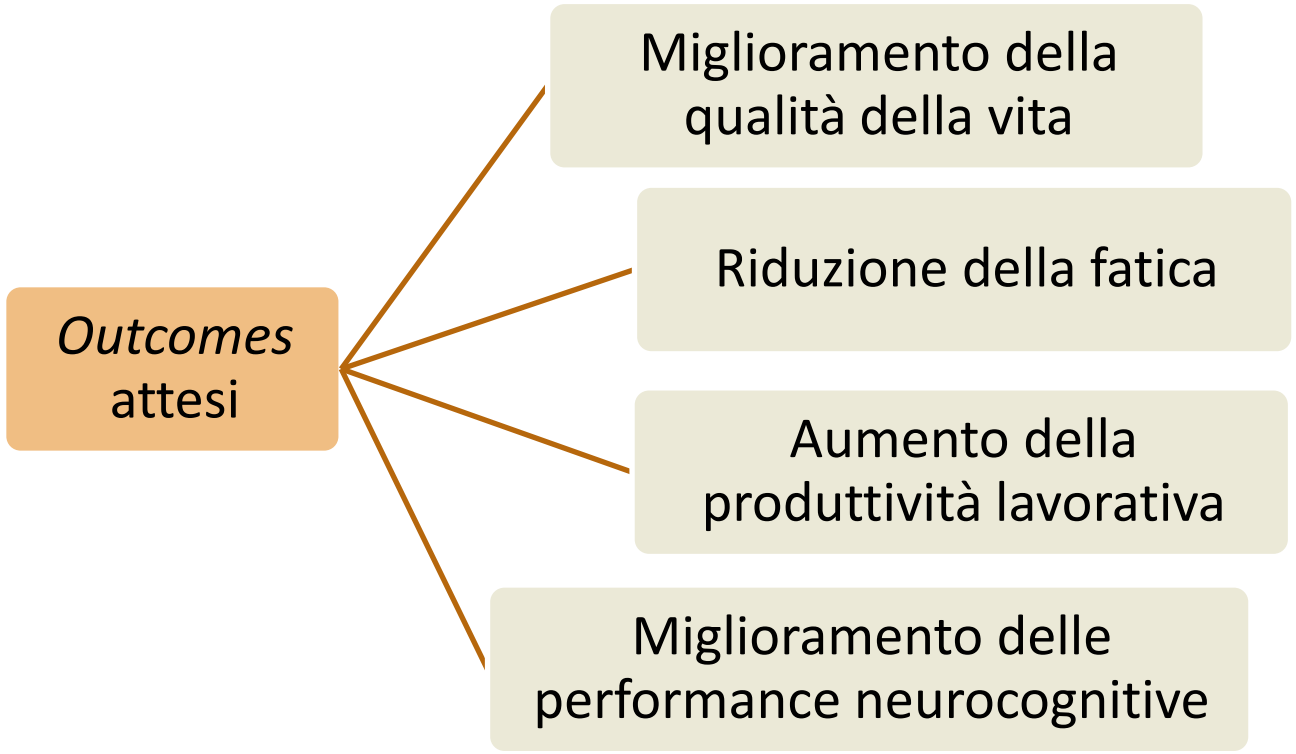
Forton et al., 2001
Monaco et al., 2015
Yarlott et al., 2016
Weissenborn et al., 2006

Esperienza clinica di real-life presso l'U.O. di Malattie Infettive degli Spedali Civili di Brescia

Terapia con DAA → **Eradicazione dell'infezione da HCV** → MIGLIORAMENTO DELLO STATO DI BENESSERE Fisico e psicologico

OBIETTIVI DELLO STUDIO

- Primario: valutare le modifiche dei **PROs** e delle **performance neurocognitive** nei pazienti con infezione cronica da HCV e trattati con DAA



- Secondario: identificare possibili **fattori** direttamente correlati con l'andamento degli *outcomes*

MATERIALI E METODI

CRITERI DI INCLUSIONE

- ✓ Pazienti con infezione da HCV trattati con DAA con follow-up di 12 settimane dalla fine del trattamento
- ✓ Età > 18 anni
- ✓ Pazienti in grado di comprendere e compilare i questionari
- ✓ Pazienti in grado di comprendere e firmare il consenso informato

CRITERI DI ESCLUSIONE

- ✓ Soggetti con infezione da HIV e nadir di CD4<200 cell/µL e/o con encefalopatia HIV correlata
- ✓ Abuso alcolico > 1L/die in atto
- ✓ Utilizzo di sostanze stupefacenti in atto
- ✓ Malattia psichiatrica grave in terapia (schizofrenia, disturbo bipolare)

MATERIALI E METODI

- Baseline – BL → stato iniziale dei pazienti
- End of Treatment – EOT → effetto immediato della terapia
- Follow-up a 12 settimane – FU12W → rapporto con SVR e andamento a distanza di tempo

L'analisi statistica è stata effettuata in collaborazione con la Sezione di Statistica Medica e Biometria del Dipartimento di Medicina Molecolare e Traslazionale dell'Università degli Studi di Brescia.

MATERIALI E METODI

Qualità della vita:

Chronic Liver Disease Questionnaire (CLDQ)

- Sintomi Addominali
- Fatica
- Sintomi Sistemici
- Attività
- Emotività
- Preoccupazione

(Z M Younossi et al., 1999)

Performance neurocognitive:

Montreal Cognitive Assessment (MoCA) test

(Nasreddine et al., 2005)

Fatica:

Fatigue Severity Scale (FSS)

Visual Analogue Fatigue Scale (VAFS)

(Rosa et al., 2014)

Produttività lavorativa:

Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

- Presenteismo
- Assenteismo
- Riduzione della produttività lavorativa
- Riduzione delle attività quotidiane

(Reilly et al., 1993)

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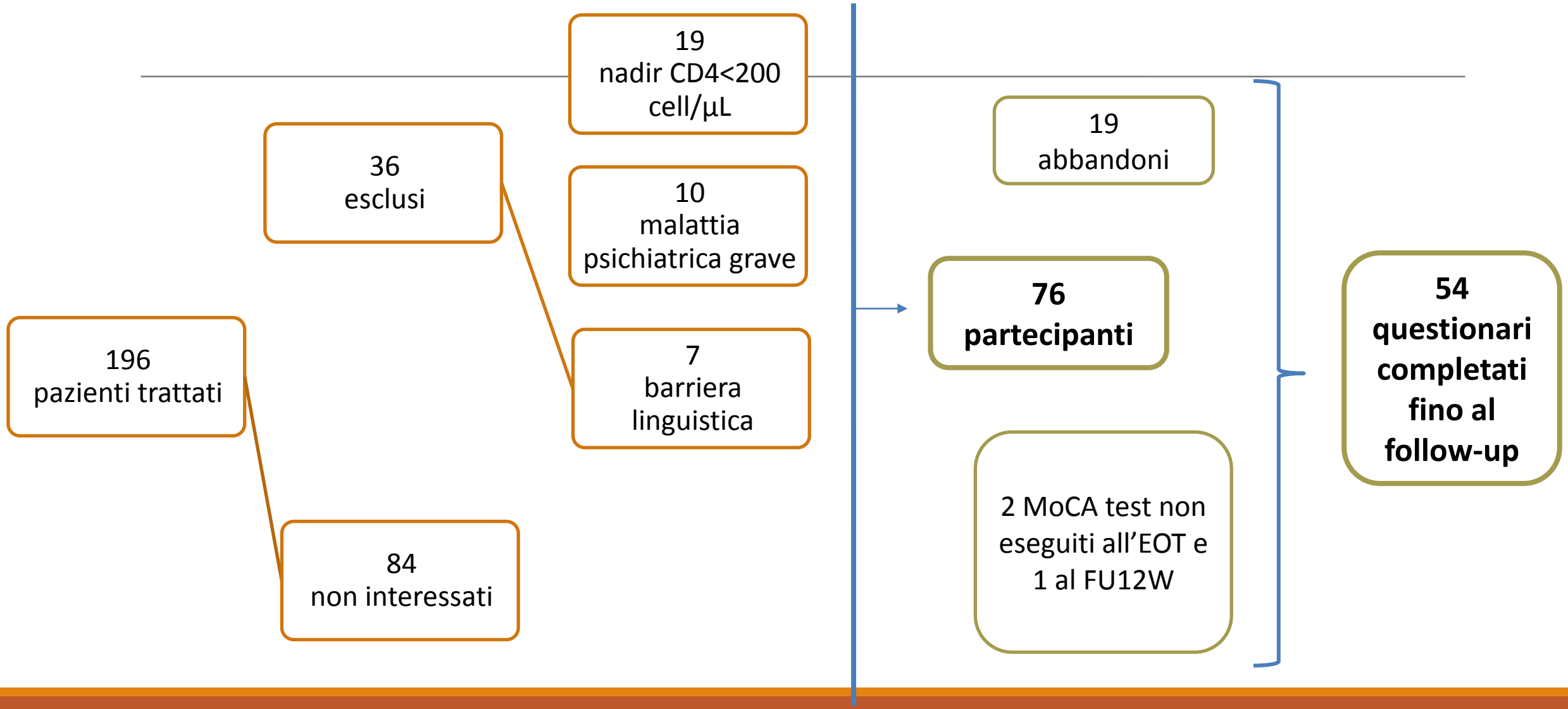
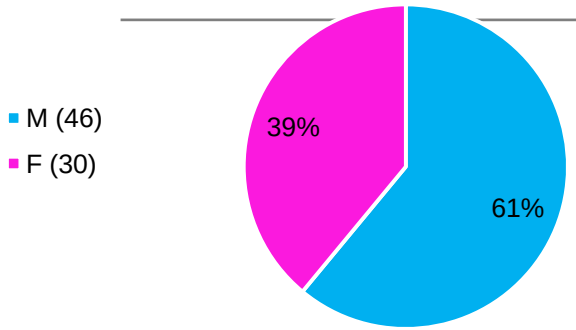
Inizio del reclutamento Ottobre 2017 - Fine del Follow-up Giugno 2018

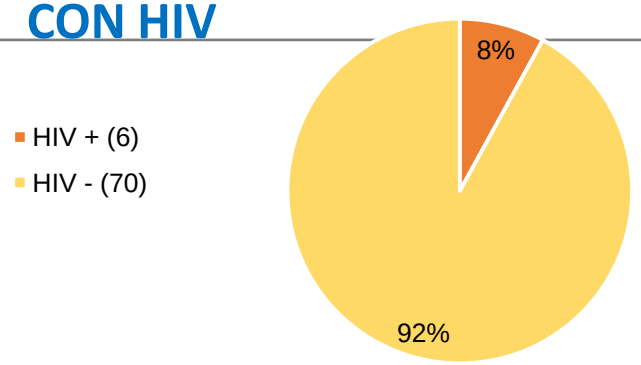


VARIABILI CONSIDERATE

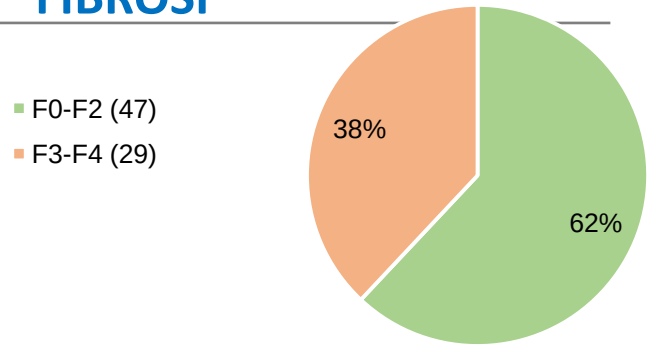
GENERE



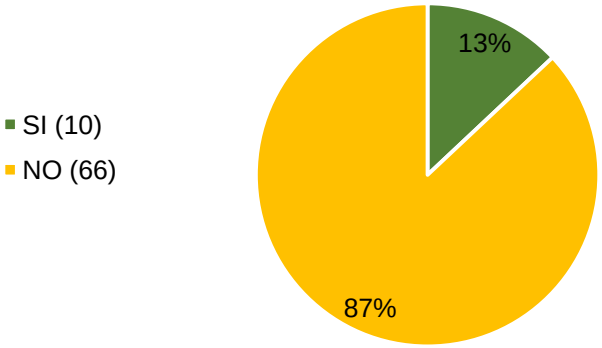
CO-INFEZIONE CON HIV



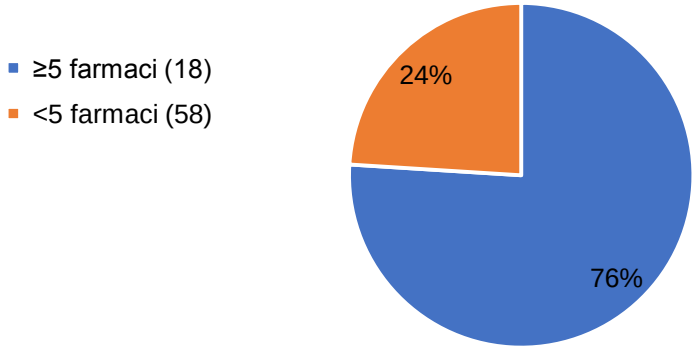
GRADO DI FIBROSI



RIBAVIRINA

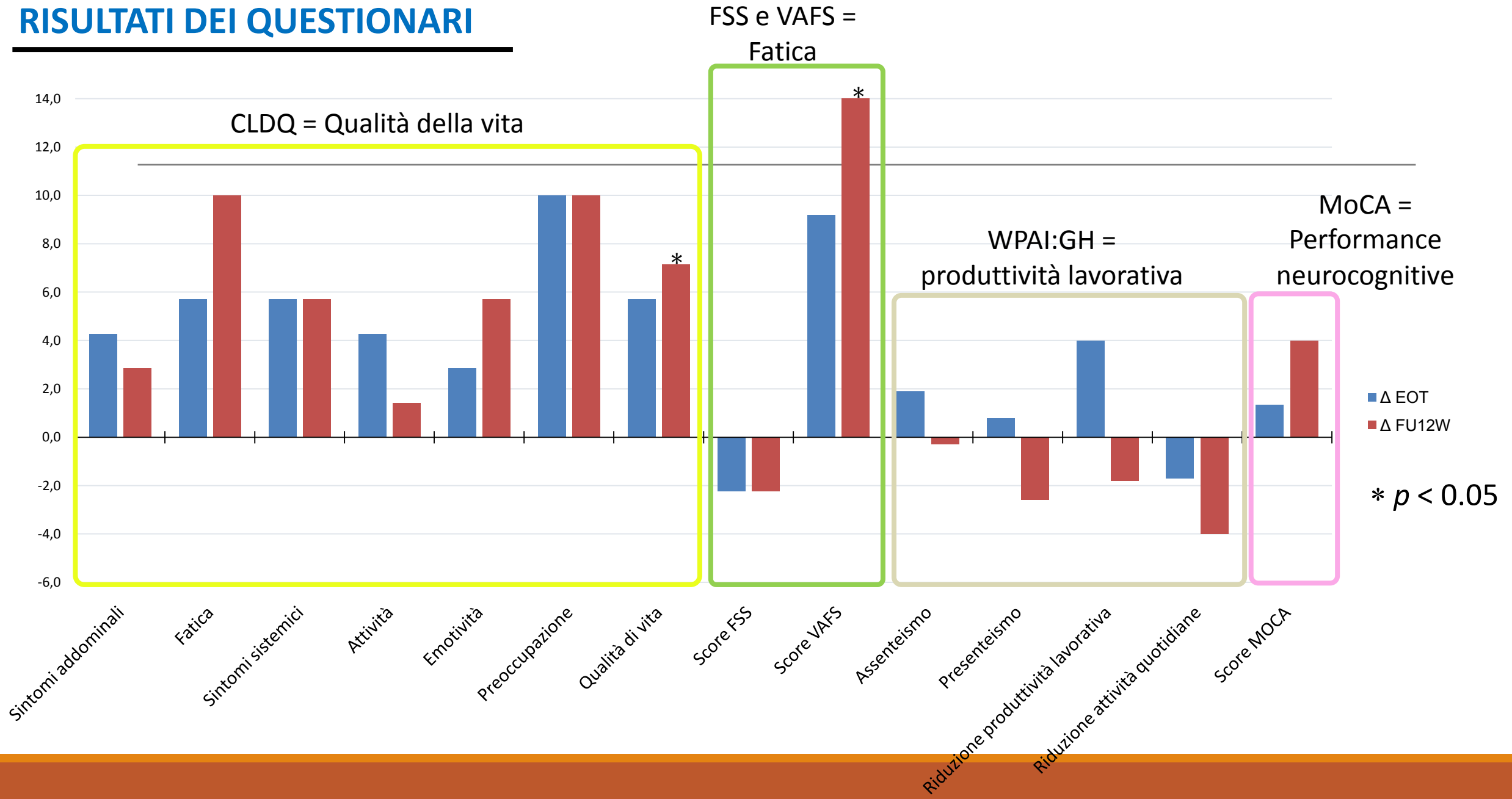


POLITERAPIA



ETÀ media 60.7 ± 13.8 anni

RISULTATI DEI QUESTIONARI



RISULTATI DEI QUESTIONARI

CLDQ → Qualità della vita

	Δ media EOT	*p-value* EOT vs BL	Δ media FU12W	*p-value* FU12W vs BL
Sintomi addominali	+0.3	0.073	+0.2	0.15
Fatica	+0.4	**0.004**	+0.7	**<0.0001**
Sintomi sistemici	+0.4	**0.0004**	+0.4	**0.003**
Attività	+0.3	**0.020**	+0.1	0.52
Emotività	+0.2	0.13	+0.4	**0.002**
Preoccupazione	+0.7	**<0.0001**	+0.7	**<0.0001**
Qualità di vita	+0.4	**<0.0001**	+0.5	**<0.0001**

RISULTATI DEI QUESTIONARI

FSS e VAFS → Fatica

	Δ media EOT	*p-value* EOT vs BL	Δ media FU12W	*p-value* FU12W vs BL
score FSS	-0.2	0.34	-0.2	0.27
score VAFS	+9.2	**<0.0001**	+14.1	**<0.0001**

Fatica: frequente e invalidante!

RISULTATI DEI QUESTIONARI

WPAI:GH → Produttività lavorativa

Produttività lavorativa migliora
Assenteismo e Presenteismo diminuiscono
→ RIDUZIONE DEI COSTI INDIRETTI

	Δ media EOT	*p-value* EOT vs BL	Δ media FU12W	*p-value* FU12W vs BL
Assenteismo	+1.9%	0.50	-0.3%	0.93
Presenteismo	+0.8%	0.71	-2.6%	0.76
Riduzione produttività lavorativa	+4.0%	0.44	-1.8%	0.74
Riduzione attività quotidiane	-1.7%	0.74	-4.0%	0.52

RISULTATI DEI QUESTIONARI

MoCA test

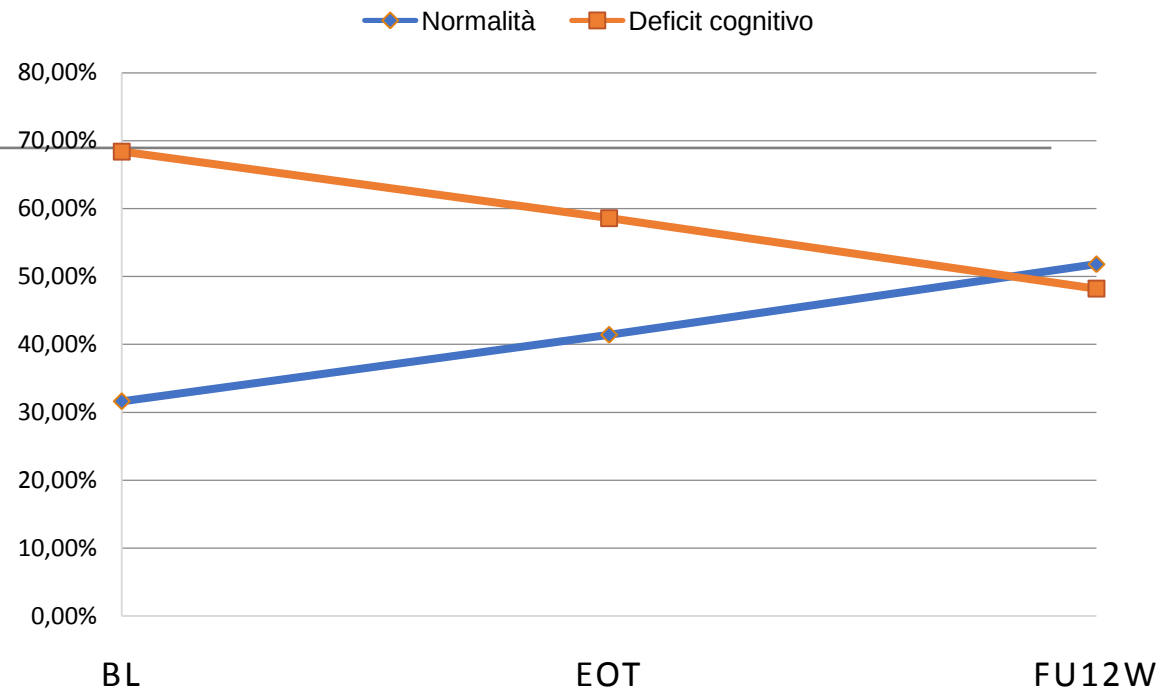
→ **Performance neurocognitive**

	Δ media EOT	*p-value* EOT vs BL	Δ media FU12W	*p-value* FU12W vs BL
Score MoCA	+0.4	0.17	+1.2	**0.0009**

RISULTATI DEI QUESTIONARI

MoCA test

→ **Performance neurocognitive**

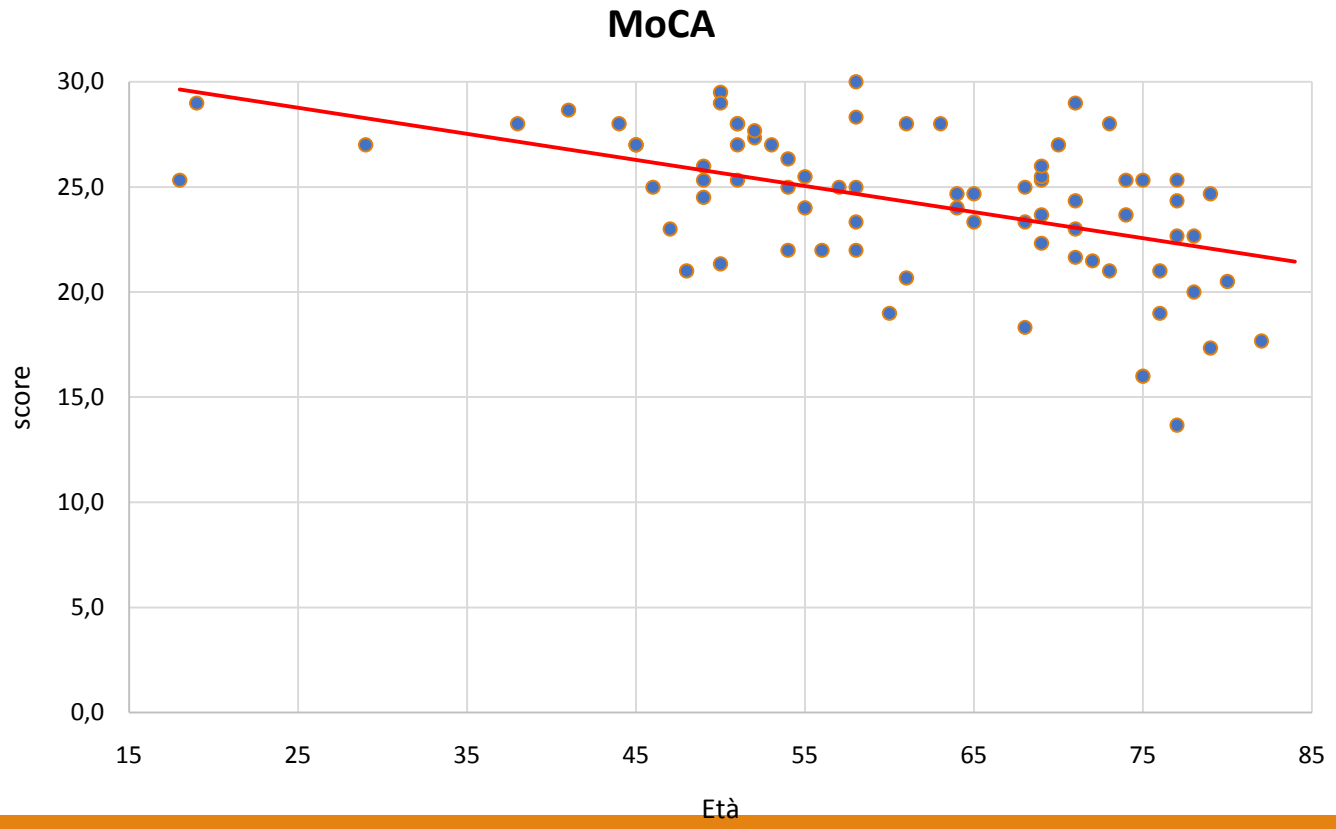


	Δ media EOT	*p-value* EOT vs BL	Δ media FU12W	*p-value* FU12W vs BL
Score MoCA	+0.4	0.17	+1.2	**0.0009**

FATTORI INFLUENTI

ETÀ
(media: 60.7 ± 13.8 anni)

All'aumentare dell'età, le performance neurocognitive peggiorano



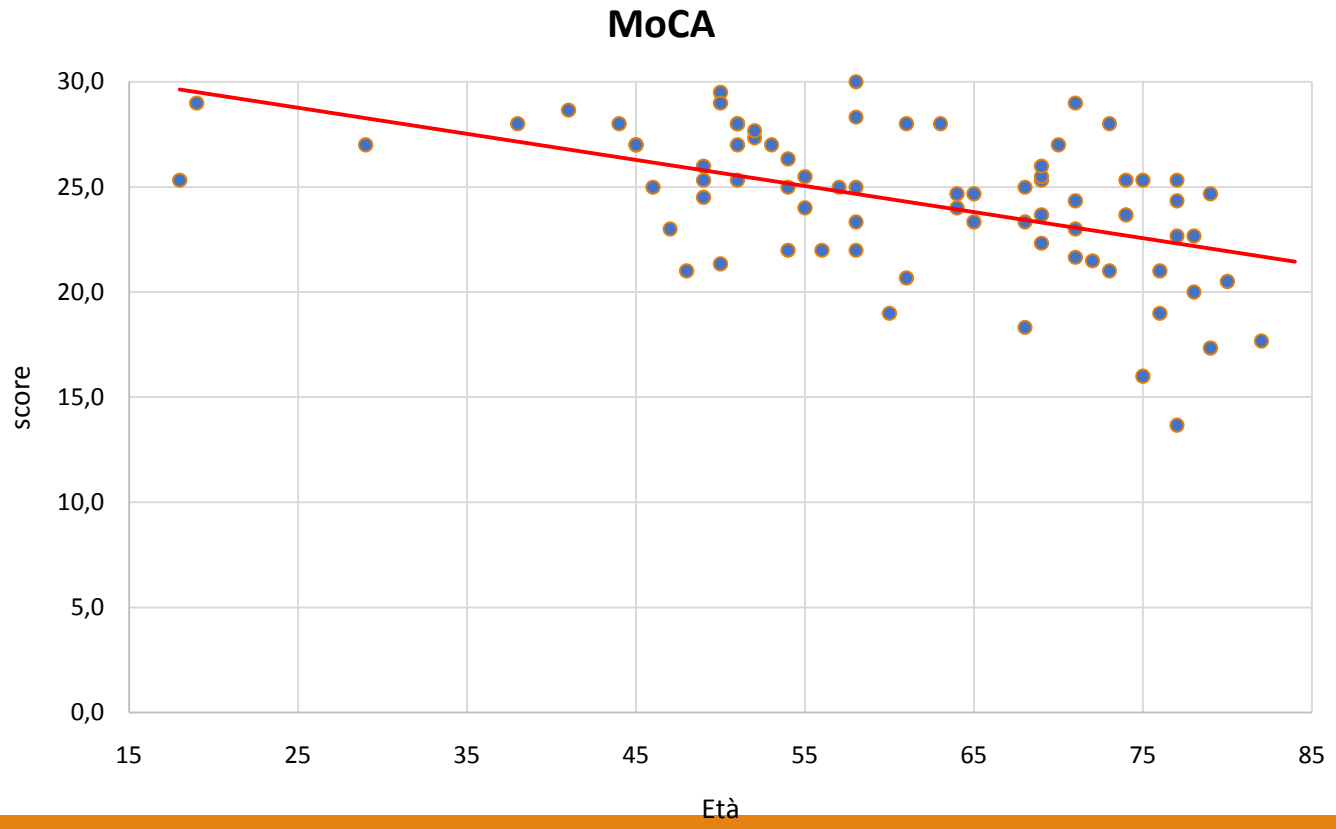
$\beta = -0.107$

$p = 0.0002$

FATTORI INFLUENTI

ETÀ
(media: 60.7 ± 13.8 anni)

All'aumentare dell'età, le performance neurocognitive peggiorano



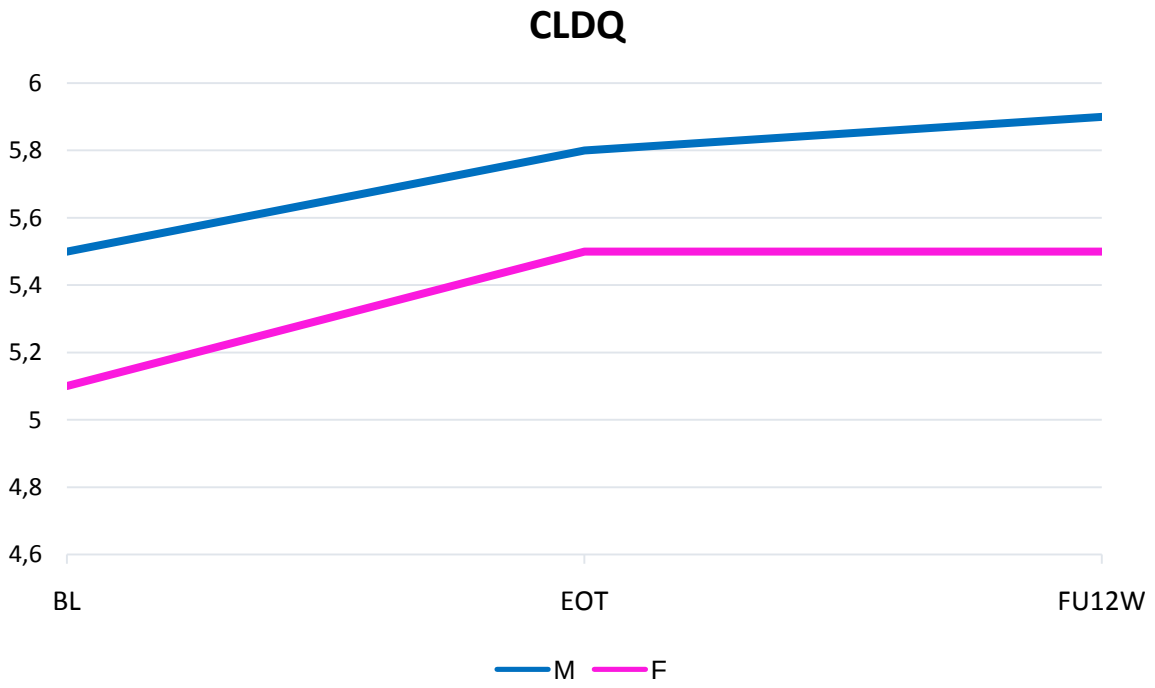
Nessuna influenza su qualità di vita e fatica

$\beta = -0.107$

$p = 0.0002$

FATTORI INFLUENTI

GENERE → *Le donne hanno una qualità di vita e delle performance neurocognitive peggiori rispetto agli uomini*

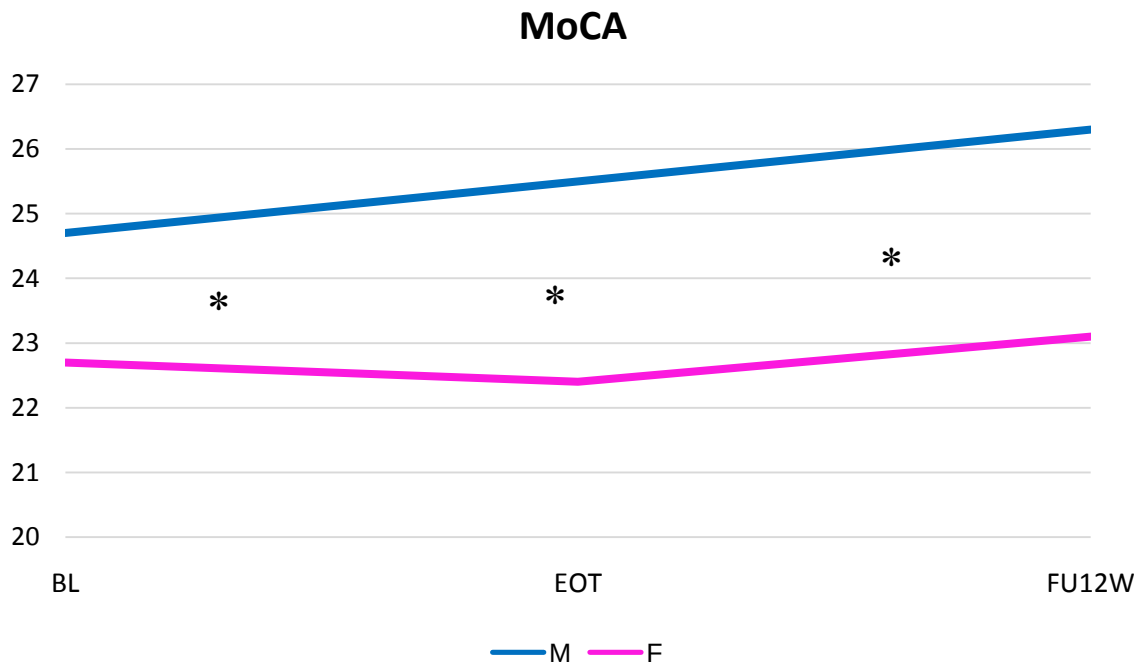


→ Concorde con la letteratura

$* p < 0.05$

FATTORI INFLUENTI

GENERE → *Le donne hanno una qualità di vita e delle performance neurocognitive peggiori rispetto agli uomini*



* $p < 0.05$

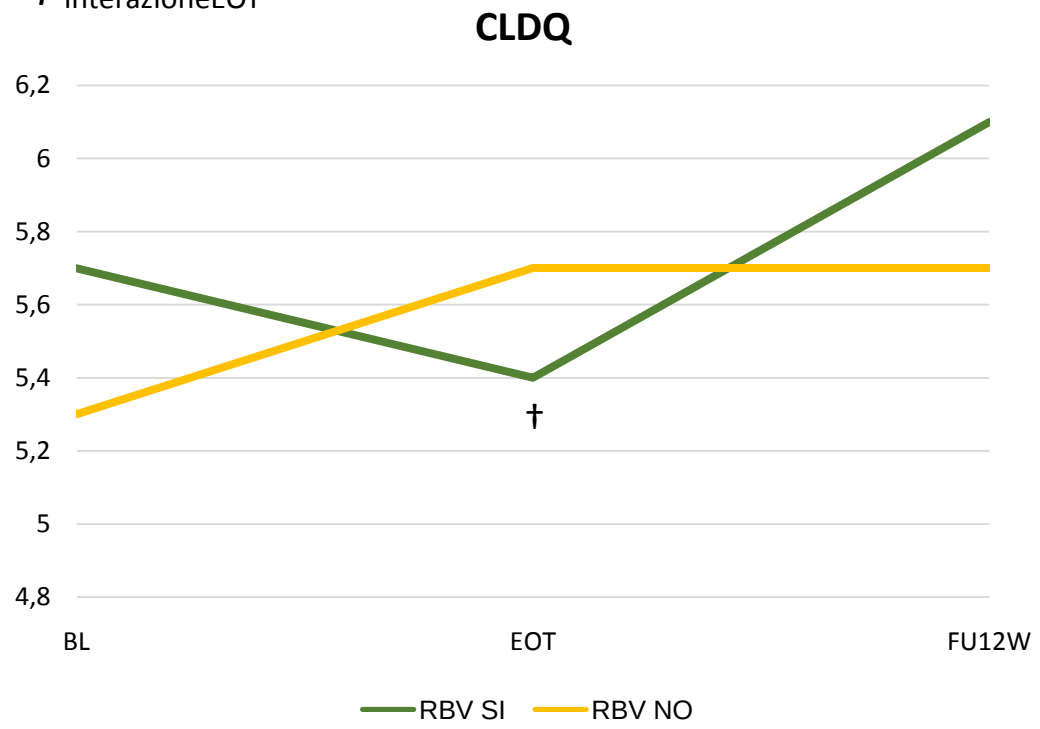
→ Nuovo riscontro

Età media:
Donne 64,1 ± 13,5
Uomini 58,4 ± 13,7

FATTORI INFLUENTI

RIBAVIRINA → *Causa un peggioramento della qualità della vita*

† $p_{interazioneEOT} = 0.003$

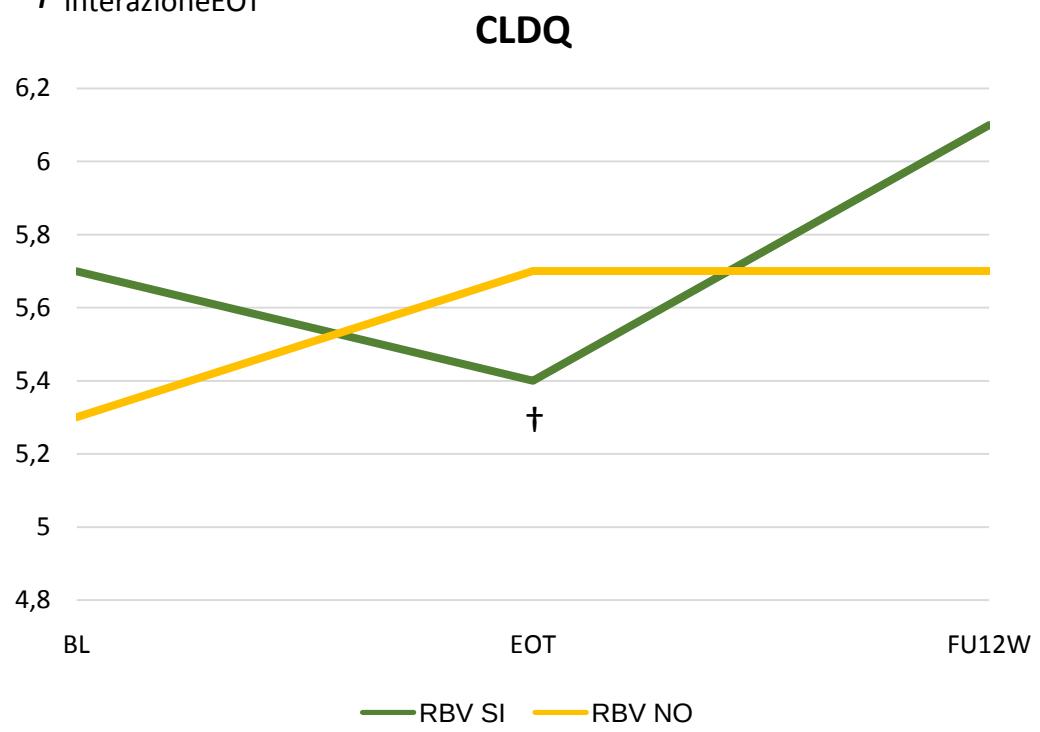


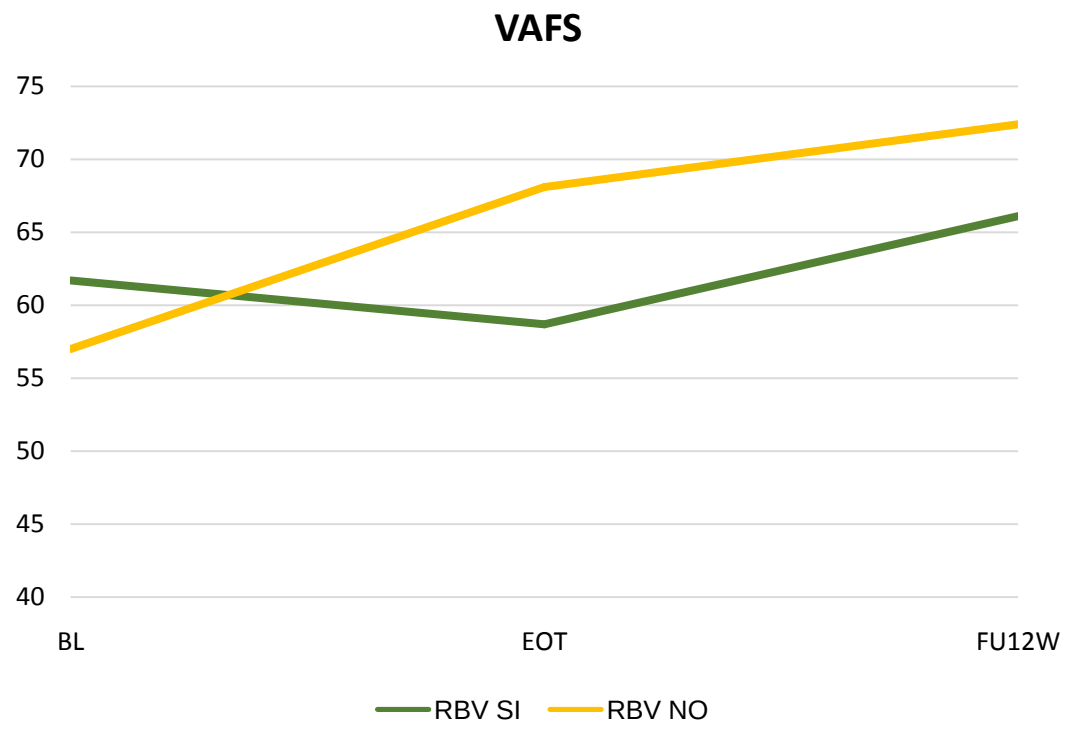
FATTORI INFLUENTI

RIBAVIRINA → *Causa un peggioramento della qualità della vita*

→ *Effetto simile sulla fatica*

† $p_{interazioneEOT} = 0.003$





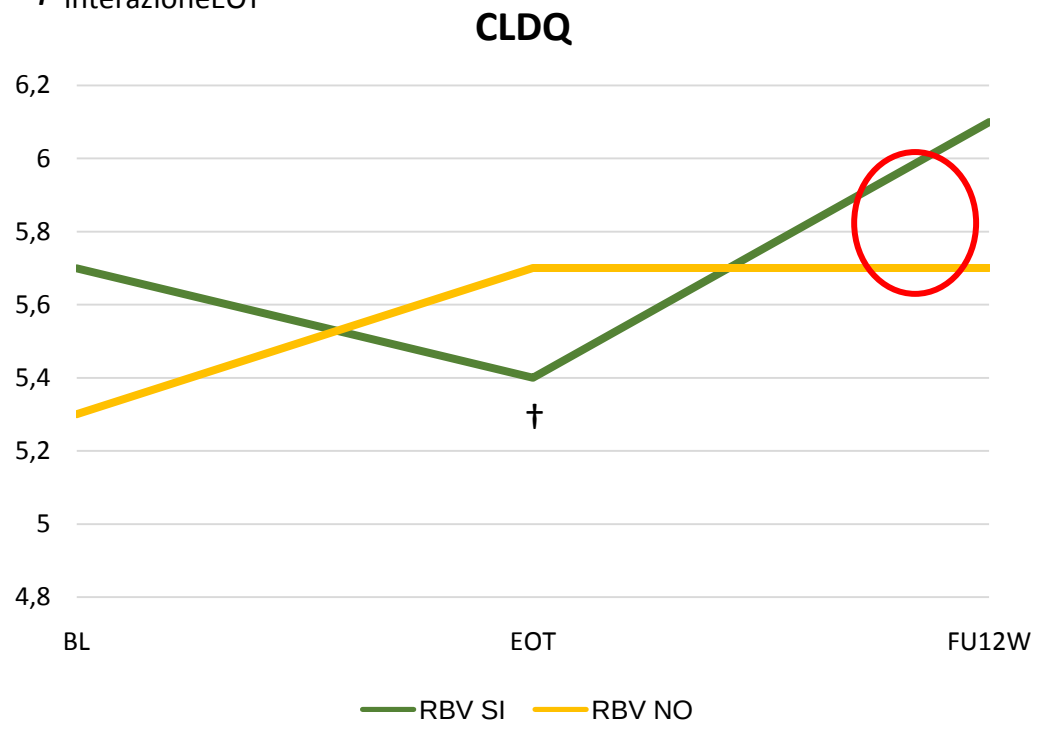
FATTORI INFLUENTI

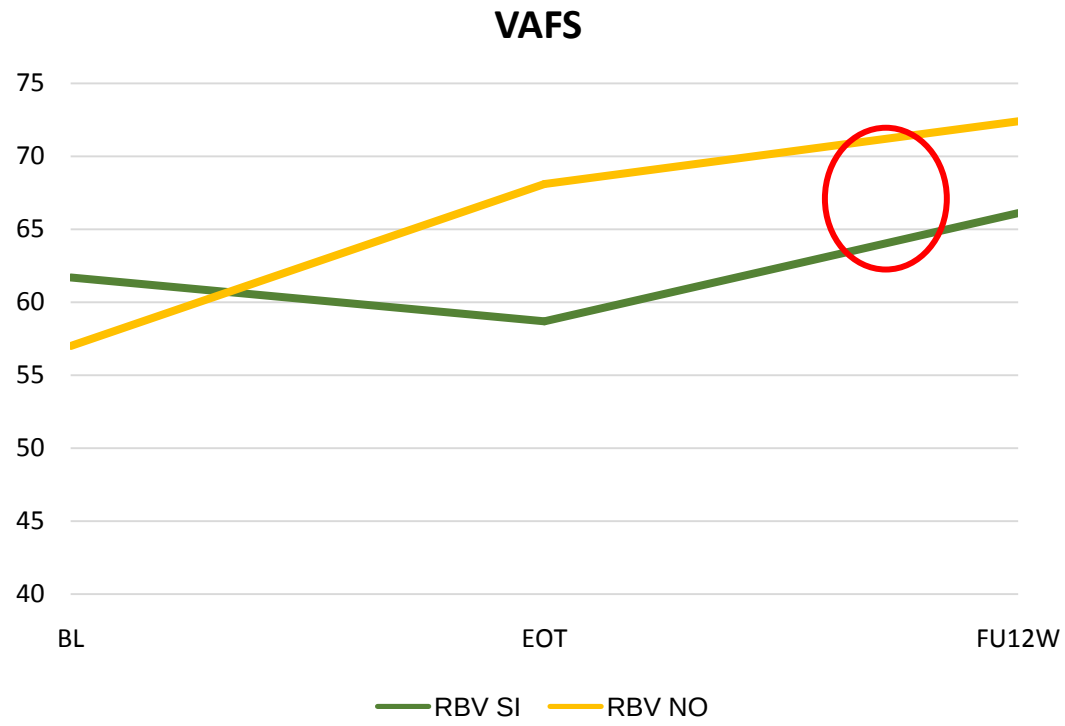
RIBAVIRINA → *Causa un peggioramento della qualità della vita*

→ *Effetto simile sulla fatica*

Effetto reversibile

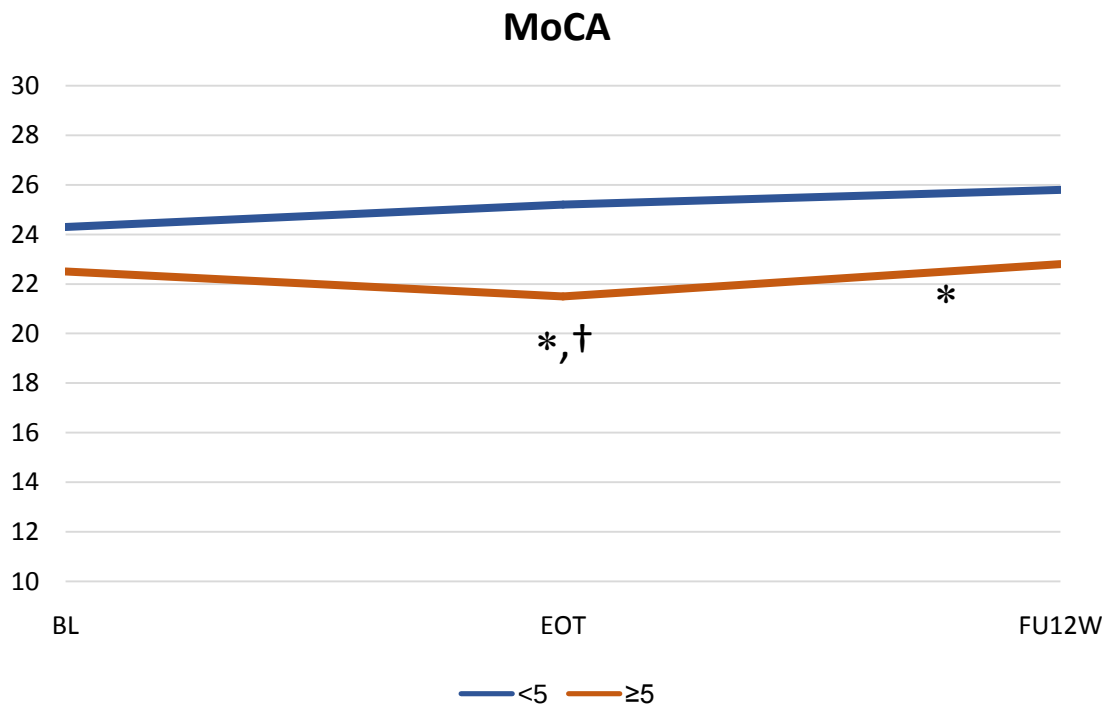
† $p_{interazioneEOT} = 0.003$





FATTORI INFLUENTI

POLITERAPIA → *Chi assume ≥5 farmaci ha peggiori performance neurocognitive*



→ In linea con altri studi

* $p < 0.05$

† $p_{interazioneEOT} = 0.013$

IL GRADO DI FIBROSI E LA CO-INFEZIONE CON HIV NON INFLUENZANO NESSUN OUTCOMES

MIGLIORAMENTO ANALOGO AL RESTO DEI PAZIENTI
DAA ben tollerati
Stessi benefici

6 CO-INFETTI HIV/HCV vs 70 MONOINFETTI HCV

DISCUSSIONE e CONCLUSIONI

TERAPIA CON DAA
alto tasso di successo e pochi effetti collaterali

Miglioramenti mantenuti e, a volte, anche aumentati nel tempo, in corrispondenza dell'SVR12

Eradicazione dell'infezione da HCV

Miglioramento della qualità della vita, della fatica e della performance neurocognitive

DISCUSSIONE e CONCLUSIONI

Importanza della valutazione dei PROs e delle performance neurocognitive per comprendere quale sia l'impatto globale dell'infezione da HCV (e della sua eradicazione) sulla salute del paziente

VALUTAZIONI DA INTRODURRE NELLA PRATICA CLINICA

COSA CI FA PENSARE TUTTO QUESTO?
STIAMO SOTTOVALUTANDO MOLTI ASPETTI?
QUALI LE POSSIBILI DIFFICOLTA'?


SERVIZIO SANITARIO NAZIONALE
REGIONE CALABRIA
Codice di esenzione
REPUBBLICA ITALIANA
TESSERA SANITARIA
Data di scadenza
Nome
Luogo di nascita
Provincia
Data di nascita
Sesso


To Be Continued

GRAZIE PER L’ATTENZIONE