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ATTUALITA' NELLA GESTIONE DEL PAZIENTE CON HCV
Il paziente con patologie extraepatiche

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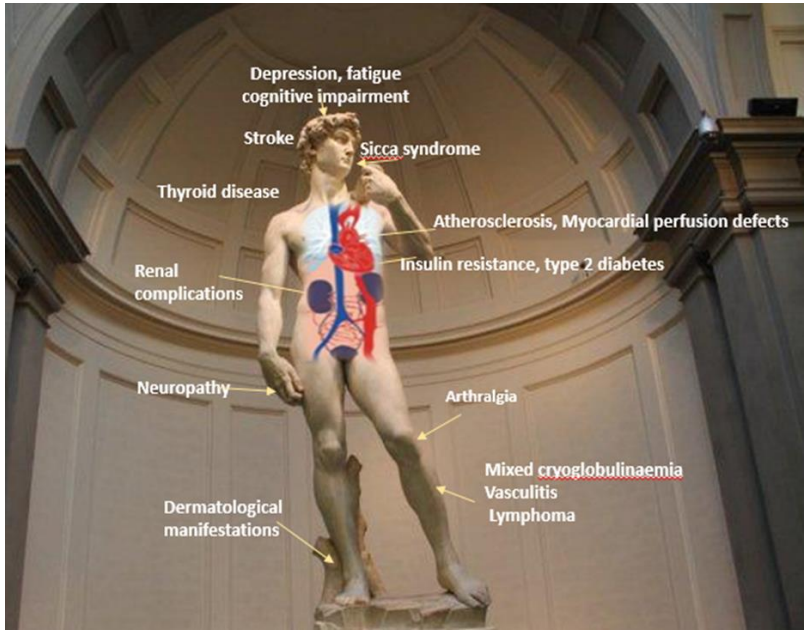
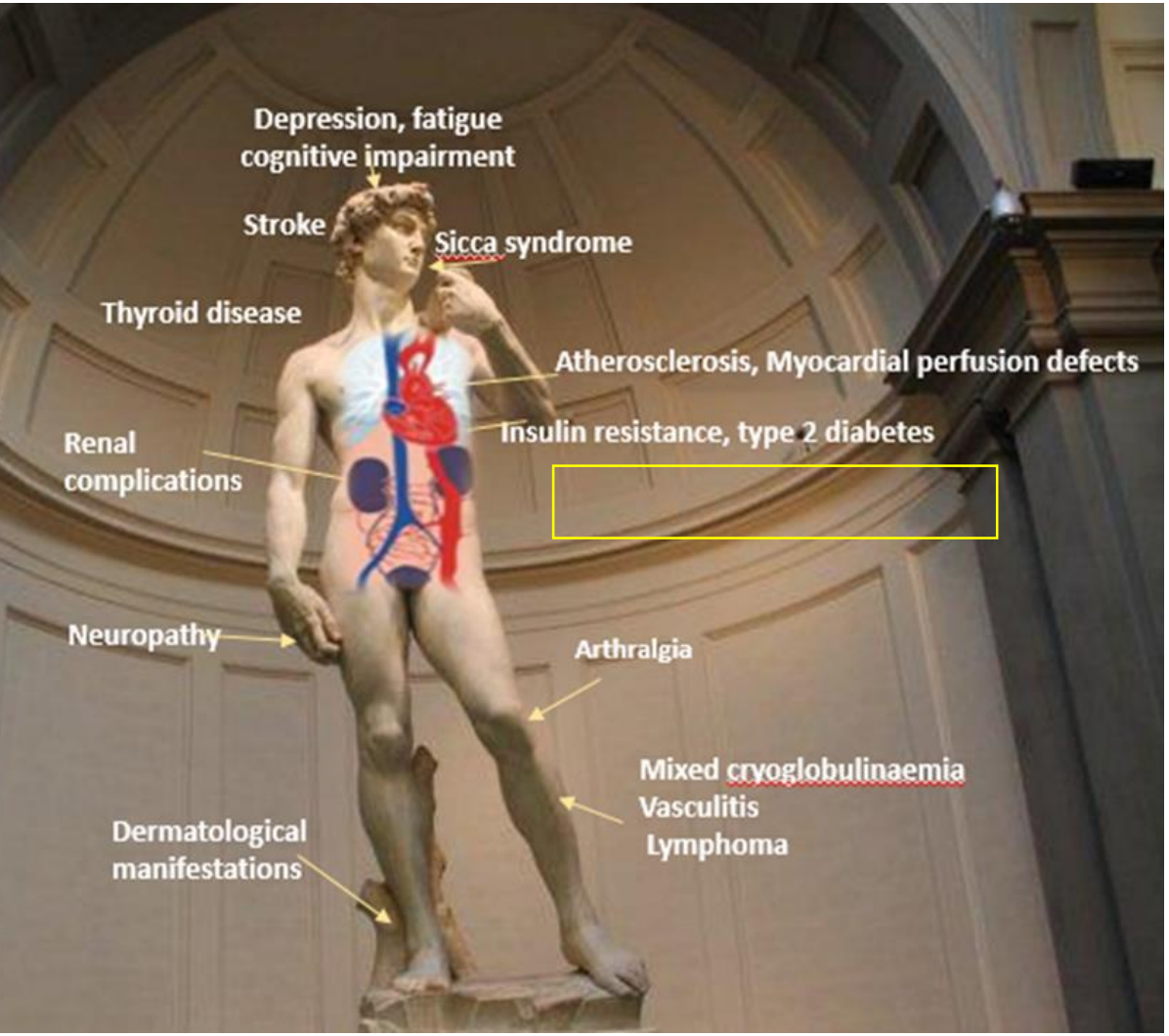
Extrahepatic Manifestations of Chronic HCV Infection



- Among all viruses, hepatotropic and nonhepatotropic, HCV is recognized as the most often associated with extrahepatic manifestations that are present in up to 2/3 of pts (1)
- Unequivocal data support a causal relationship between HCV and some of these disorders, including MCS (CV), lymphoma, cardiovascular diseases, insulin resistance, and type 2 DM, all of which can substantially affect morbidity, mortality, and quality of life (1)
- MCS is a multifaceted disorder that mimics most HCV EHMs and HCV infection may trigger multiple pathogenetic alterations that are responsible for autoreactive, lymphoproliferative, and neoplastic disorders (2)
- The different HCV EHMs phenotypes may be the consequence of multistep and multifactorial pathogenetic processes. Both environmental and genetic factors may alter the disease progression from asymptomatic HCV infection to the most severe complications (2)

1. P Cacoub, D Saadoun. N Engl j Med, 2021; 2. Ferri C, Zignego AL, Antonelli A. N Engl j Med, 2021

Type 2 Diabetes



Increased incidence of type 2 DM among HCV patients (probably due to direct viral effects, insulin resistance, release of proinflammatory cytokines, and other immune mediated processes)

After AVT:

-reduced incidence of complications of diabetes (acute coronary syndrome, ESRD, ischemic stroke, retinopathy)

-significant improvement in glycemic control both in patients without DM (insulin resistance and insulin level) and in those with DM (blood glucose and glycated hemoglobin levels)

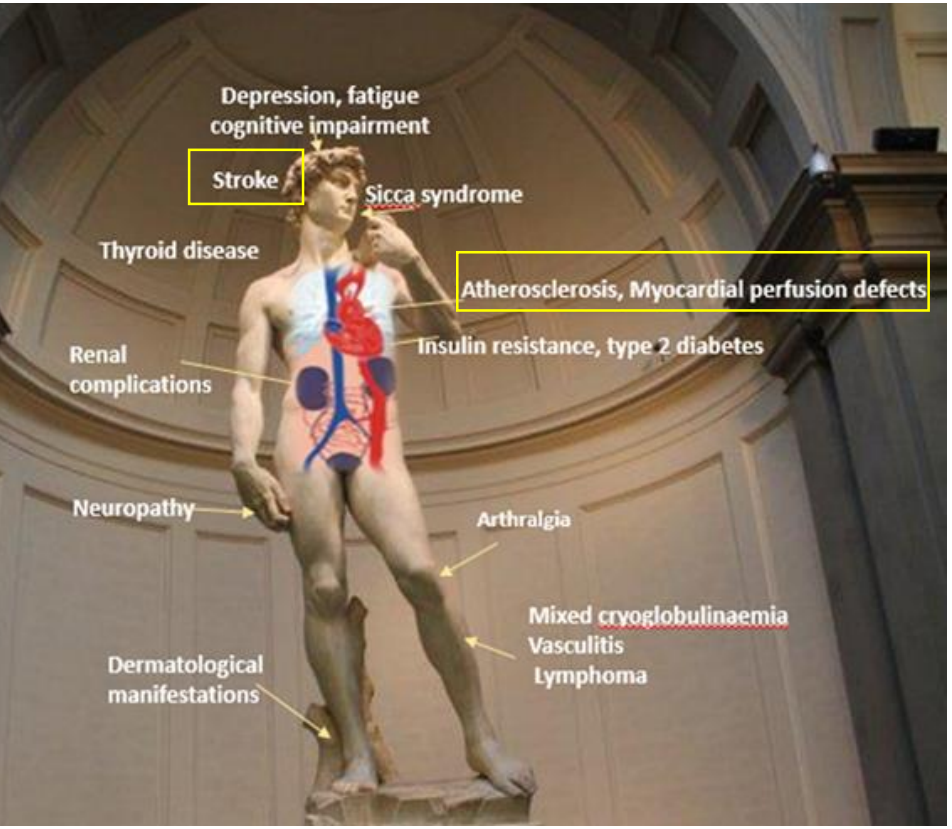
-reduced incidence of DM, as compared with IFN-treated or untreated controls in patients treated with DAAs (21,279 nondiabetic HCV U.S. veterans database)

-a reduced dose or discontinuation of oral hypoglycemic agents or insulin therapy has been reported:

Diabetic patients receiving DAAs should be closely monitored for reduction of antidiabetic drugs, to avoid hypoglycemic events.

Cacoub P et al GUT 2018, NEJM 2021; *Zignego et al. Autoimmun Dis 2017; Valenti et al, Hepatol commun 2021; Cacciola et al, J Virol 2020;* Takahashi et al, JGH Open. 2020;Adinolfi et al, *Diabetes Obes Metab. 2020*

Cardio/Cerebro-vascular Events



- Available data justified the inclusion of HCV infection among the modifiable risk factors for cardiovascular disease (including stroke, myocardial infarction, coronary artery disease, peripheral arterial disease, myocarditis, and heart failure)

- A significant association between HCV infection and cardiovascular or cerebrovascular events after adjustment for cardiometabolic confounders was confirmed in a meta-analysis

<u>After AVT:</u>

The association between DAA therapy and a decrease in the rates of overall cardiovascular events or cerebrovascular and cardiac events was greater than the one observed using IFN-based therapy

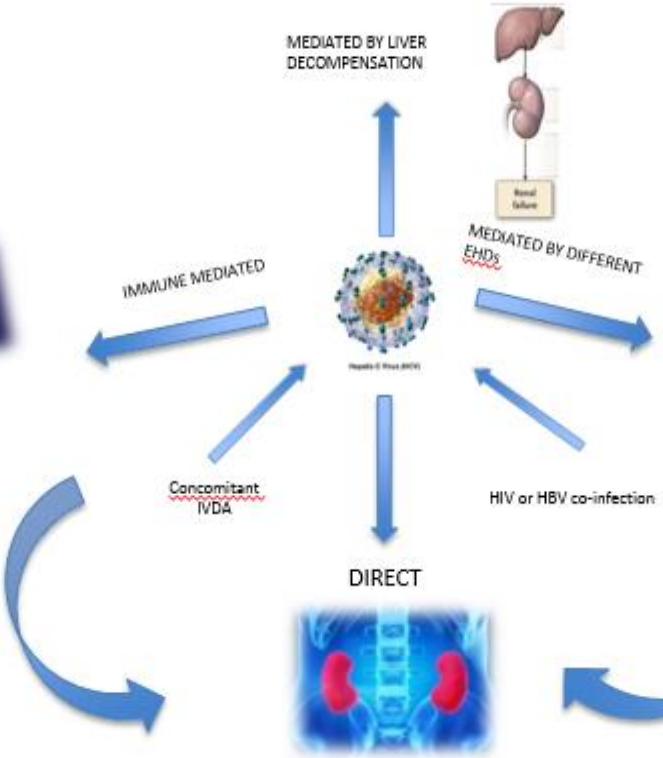
Ishizaka N, Lancet 2002; Ishizaka N, Circ J 2003, Boddi et al, Dig Liver Dis 2007 and J Clin Virol. 2010, Petta S, Gastroenterology 2016, Cacoub NEJM 2021, Zignego Autoimmun Dis 2017; Vassalle C, Hearth 2004; Lee MH, Stroke 2010; Lee MH, JID 2012; Guiltinam AM, J Epidemiol 2008; Hsu CS, et al. APT 2013; Petta S et al, Hepatology 2018; Butt et al, Gastroenterology 2019

Chronic Kidney Disease

- HCV infection has been implicated as a modifiable risk factor for CKD (in a meta-analysis the estimated risk of CKD was increased by a factor of 1.2)
- HCV-associated renal involvement related to a type I membranoproliferative glomerulonephritis is frequently reported (with up to 55% of patients affected by CV); other forms include non-CV membranoproliferative glomerulonephritis, membranous nephropathy, tubulointerstitial injury

<u>After DAAs a stabilization or GFR increase rather than a normalization of renal function was frequently reported</u>

Glomerular injury may result from deposition of circulating immune complexes of HCV, anti-HCV, and rheumatoid factor at the site of injury

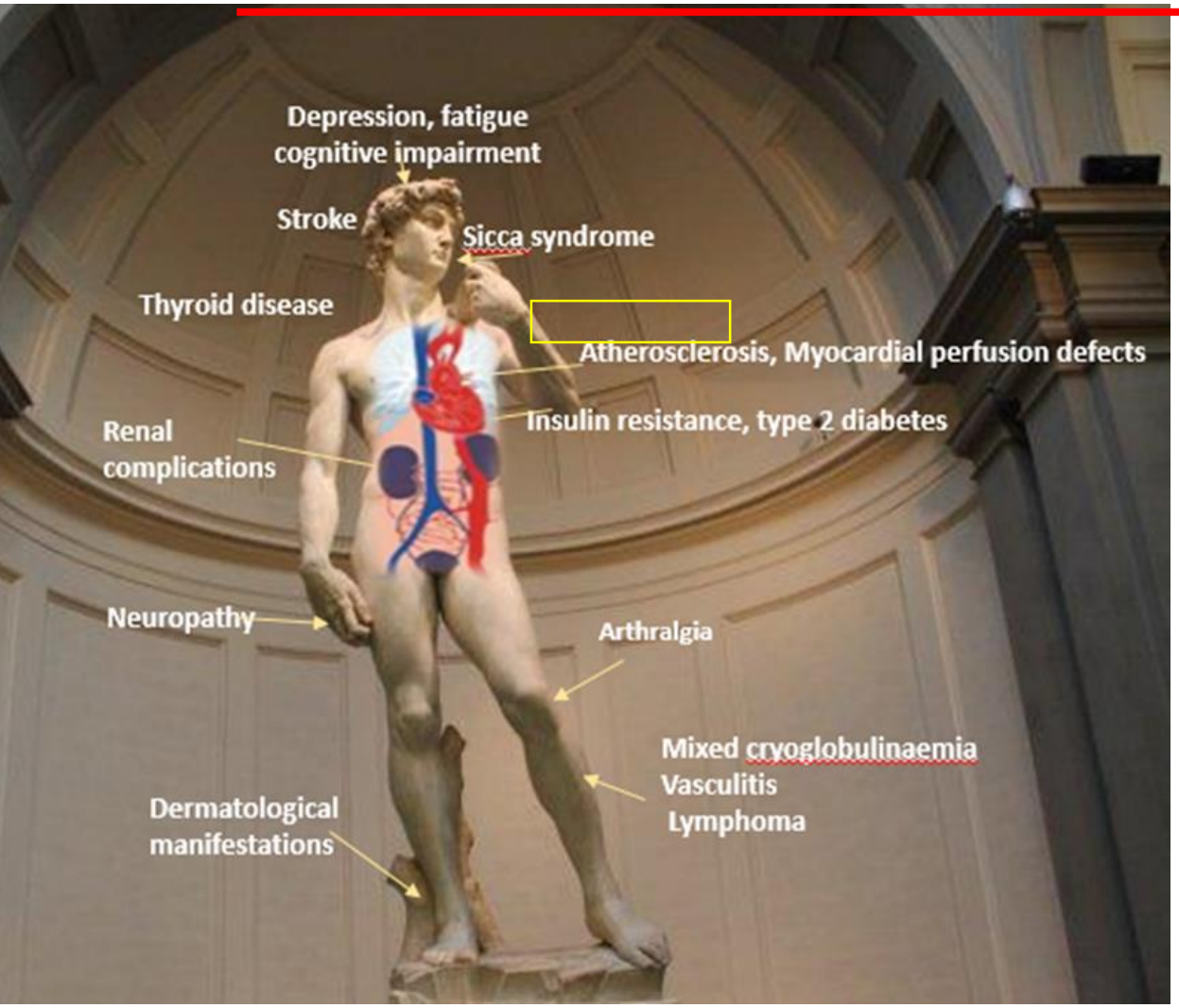


Conventional risk factors for CKD are exacerbated by HCV infection:

- Atherosclerosis
- CVD
- Diabetes mellitus type 2
- Metabolic syndrome

Zignego et al, Autoimmun Dis. 2017 ; Minutolo et al, J Nephrol and Dis Liver Dis 2018; Roccatello et al, Nat Rev Dis Primers. 2018

Sicca Syndrome (SS)



- SS symptoms have been reported in 20 to 30% of patients with HCV infection, whereas less than 5% of patients with a defined Sjögren's syndrome (pSS) are HCV-positive (ie, antibodies against Ro(SSA), La(SSB) neg)

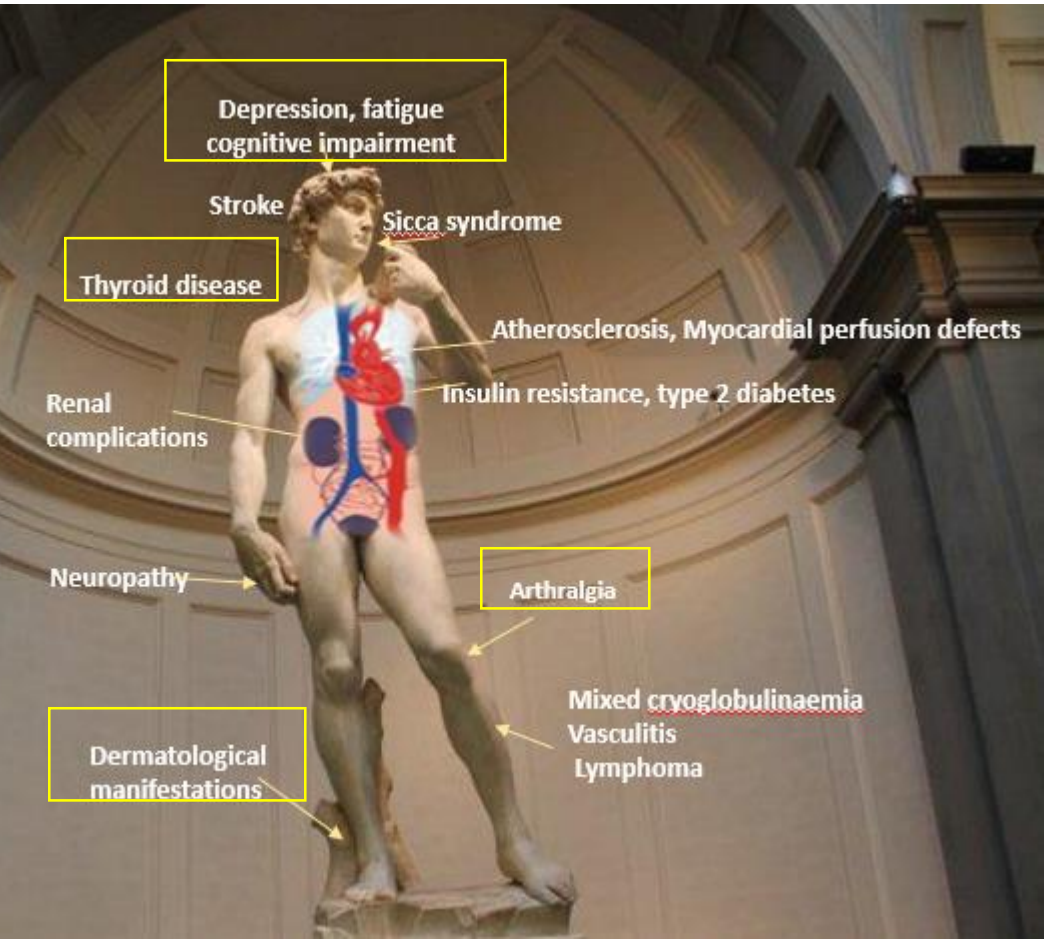
- In a meta-analysis of 5 cross-sectional and 5 cohort studies, a significant positive relationship between HCV infection and development of SS was found, the pooled random effects OR being 3.31 (95% CI, 1.46-7.48; P < 0.001).

SS and Viruses: a very interesting association

recent Identification of HDV in pSS patients and induction of a complete pSS-like phenotype further support a viral-mediated etiopathology of pSS

Wang et al, Microbiol Immunol 2014; Weller et al Pathog Immun 2016; Zignego et al Autoimmun Rev 2017; Cacoub et al, NEJM 2021

OTHER EHMs HCV



Autoreactivity: the prevalence of autoantibodies is high, the most common being RF (in 70% of patients), followed by ANA (20 to 40%), anticardiolipin ab (15%), anti-thyroid ab (12%), and ASMA (7%).

Arthralgia (rarely with arthritis) and **myalgia** have frequently been reported in HCV patients, mostly in the context of CV (usually no evidence of joint destruction (RA-like) and anti–cyclic citrullinated peptide)

Autoimmune Hemolytic anemia and thrombocytopenia, **dermatological manifestations** (lichen planus and porphyria cutanea tarda), and **hypothyroidism**

Neuropsychiatric manifestations: high prevalence among HCV patients; proton magnetic resonance spectroscopic studies showed that HCV patients, even those without advanced liver disease, have altered cerebral metabolism

Wilkinson J et al. J Virol 2009 83(3): 1312–1319; Negro F et al, Gastroenterology 2015; 149(6):1345-60; Younossi Z et al, J Hepatol 2016; Gragnani et al, Aliment Pharmacol Ther. 2018;. Forton D et al., Lancet 2001;; Younossi Z et al, J Hepatol 2016; Cacoub P et al, Dig Liver Dis. 2014; 46 Suppl 5:S165-73. Negro F, et al. Gastroenterology 2015;149(6):1345-60; Lucaciu LA, Dumitrascu DL. Ann Gastroenterol 2015; 28(4):440-7

Clinical Rheumatology (2022) 41:147–157
https://doi.org/10.1007/s10067-021-05877-3

ORIGINAL ARTICLE

Rapid improvement of psychiatric stigmata after IFN-free treatment in HCV patients with and without cryoglobulinemic vasculitis

Laura Gragnani[1] · Serena Lorini[1] · Lorenzo Martini[1] · Cristina Stasi[1] · Marcella Visentini[2] · Luisa Petraccia[1] · Niccolò Marello[1] · Monica Monti[1] · Silvia Marri[1] · Francesco Madia[1] · Valdo Ricca[3] · Anna Linda Zignego[1]

- HCV causes quality of life impairment and neuropsychiatric disorders, especially in patients with CV
- Limited information exists regarding the outcome of psychiatric disorders after DAAs
- 76 DAA-treated HCV-patients were prospectively studied using 4 psychometric scales to assess depression (HAM-D and MADRS), anxiety (HAM-A), and mania (MRS) as well as Short-Form-36 questionnaires evaluating quality of life

- At baseline, depression and anxiety, from mild to severe, were frequently shown, with the most advanced cases in CV group; no patients achieved the scores for mania
- A significant improvement emerged for all the psychometric scales in the entire population and in the subgroups, after viral eradication even in the short-term outcome. The Short-Form-36 summary components confirmed benefits

After HCV eradication, the depression and anxiety scores significantly improved and severity grade generally lowered
DAA-positive effects on mental disorders should be considered part of the therapy outcome, being beneficial especially in CV patients who usually have worse baseline mental scores

National and International Recommandations

DAA-base treatment should be initiated without delay for patients with EHMs HCV

Patients with CV were rated as the highest-priority patients to treat among patients with EHMs

AASLD-IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. (Updated 21 September 2017. Accessed 9 January 2018.) Available from http://www.hcvguidelines.org

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017; 66:153–194.

Documento di indirizzo dell' AISF per l'uso razionale dei farmaci anti-HCV disponibili in Italia Aggiornamento del 14 Dicembre 2020

Zignego AL, Ramos-Casals M, Ferri C, *et al*. International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. *Autoimmun Rev* 2017; 16:523–541.

Post-SVR Follow-Up of EHMs HCV: Very limited indications

EASL recommendations on treatment of hepatitis C: Final update of the series☆

Post-treatment follow-up of patients who achieve an SVR

In patients without cirrhosis who achieve an SVR, the HCV infection can be considered as definitively cured. Patients with pre-existing cofactors for liver disease (notably, history of excessive alcohol drinking, obesity and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment, as needed.

Patients with advanced fibrosis (METAVIR score F3) and patients with cirrhosis (F4) who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (though first variceal bleed is seldom observed after SVR unless additional causes for ongoing liver damage are present and persist). In patients without varices at baseline, annual monitoring of platelet counts and transient elastography assessment allows for individualised monitoring with endoscopy. If platelet counts remain above 150,000 and elastography values <20 kPa, there is no need to perform endoscopy.[377] The presence of cofactors for liver disease, such as a history of alcohol drinking or a metabolic syndrome associated with obesity and/or type 2 diabetes, may make additional assessments necessary. Long-term post-SVR follow-up studies showed that the risk of developing HCC remains in patients with cirrhosis who eliminate HCV, although it is significantly reduced compared to untreated patients or patients who did not achieve an SVR.[6,9,10,12–17,250,378] Thus, the duration of HCC surveillance in patients with advanced fibrosis or cirrhosis who achieve an SVR is indefinite.

Sorveglianza Post-SVR: Pazienti con Fibrosi Assente, Lieve o Moderata

- I pazienti con fibrosi epatica assente o lieve-moderata e senza comorbidità al basale pre-terapia antivirale, a causa della bassissima probabilità di progressione della malattia epatica e di sviluppo di HCC, non hanno indicazioni a proseguire con il follow-up epatologico.
- I pazienti con fibrosi epatica assente o lieve-moderata al basale pre-terapia antivirale e che presentino comorbidità di danno epatico (es. sindrome metabolica, obesità, steatosi epatica, abuso alcolico, sovraccarico di ferro, autoimmunità, coinfezioni virali) rimangono a rischio di progressione della fibrosi. Si consiglia monitoraggio non invasivo della fibrosi epatica annuale tramite esecuzione di esami biochimici riguardanti la funzionalità epatica, del Fibroscan e di una ecografia addome superiore.
- I pazienti con manifestazioni extraepatiche da HCV (sindrome crioglobulinemica), indipendentemente dalla presenza di cofattori di danno epatico, necessitano di periodico controllo specialistico ambulatoriale.

23

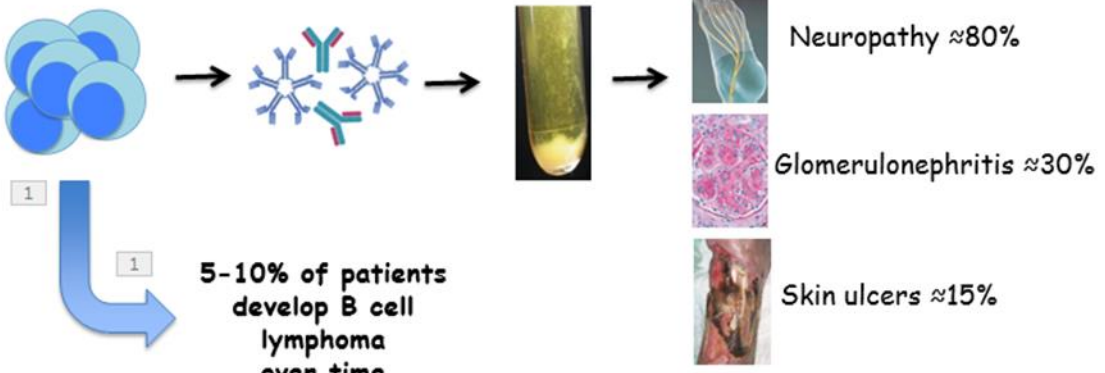
http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2018.aspx

Mixed Cryoglobulinemia-MC

- MC is an autoimmune/lymphoproliferative disorder
- HCV induces monoclonal expansion of B cells producing RF that forms these cryoprecipitable immune complexes
- Cryoglobulins can cause systemic vasculitis in the small/medium-sized vessels leading to the clinical manifestations of MC (CV)
- 40-60% of HCV+ patients harbor circulating cryoglobulins; 5-30% with MCS/CV manifestations

Mixed cryoglobulinaemia vasculitis

Clinical	Serological
• Purpura	• Mixed cryoglobulins
• Weakness	• RF+
• Arthralgias	• Low C4
• Liver involvement	**Pathological**
• Renal involvement	• Leukocytoclastic vasculitis
• Skin involvement	• B cell expansion
• Peripheral neuropathy	

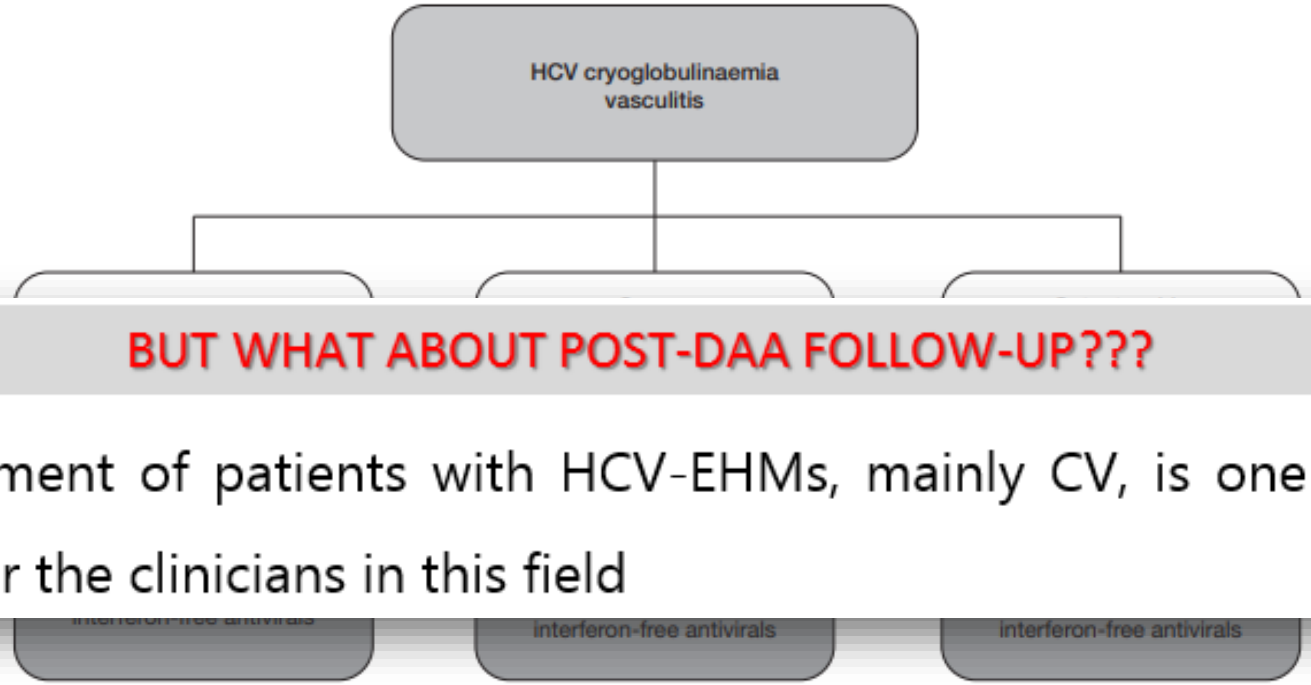


Expert opinion on managing chronic HCV in patients with mixed cryoglobulinaemia vasculitis

*Anna Linda Zignego[1], Jean-Michel Pawlotsky[2,3], Mark Bondin[4], Patrice Cacoub[5,6,7,8]**

Antiviral Therapy 2018;

Proposed treatment algorithm for HCV-associated mixed cryoglobulinaemia vasculitis |



BUT WHAT ABOUT POST-DAA FOLLOW-UP???

- The management of patients with HCV-EHMs, mainly CV, is one of the residual challenges for the clinicians in this field

Management of HCV CV should be individualized according to the severity of CV:

- Patients with mild-moderate CV should be treated only with DAAs
- In severe cases , RTX should also be administered, with plasmapheresis if necessary
- CS may be used to help control of minor inflammatory symptoms, whereas other immunosuppressant should only be given in cases of refractary CV

HEPATOLOGY AASLD 16 December 2021 | https://doi.org/10.1002/hep.32281

A prospective study of DAA Effectiveness and Relapse Risk in HCV Cryoglobulinemic Vasculitis by the Italian PITER Cohort

Loreta A Kondili, Monica Monti, Maria Giovanna Quaranta, Laura Gragnani, Valentina Panetta, Giuseppina Brancaccio, Cesare Mazzaro, Marcello Persico, Mario Masarone, Ivan Gentile, Pietro Andreone, Salvatore Madonia, Elisa Biliotti, Roberto Filomia, Massimo Puoti, Anna Ludovica Fracanzani, Diletta Laccabue, Donatella Ieluzzi, Carmine Coppola, Maria Grazia Rumi, Antonio Benedetti, Gabriella Verucchi, Barbara Coco, Liliana Chemello, Andrea Iannone, Alessia Ciancio, Francesco Paolo Russo, Francesco Barbaro, Filomena Morisco, Luchino Chessa, Marco Massari, Pierluigi Blanc, Anna Linda Zignego

.Total PITER HCV+ patients: 11.871

.HCV+ patients evaluated: 3390 (28,5%)

.Cryoglobulinemic patients: 1255 (37%)

. with symptoms: CV 523/1255 (41,7%)

. asymptomatic: MC 732/1255 (58,3%)

- Type III in 33%
- Type II in 67%

Clinical response (FCR, CR, PR):
88% at one time of FU

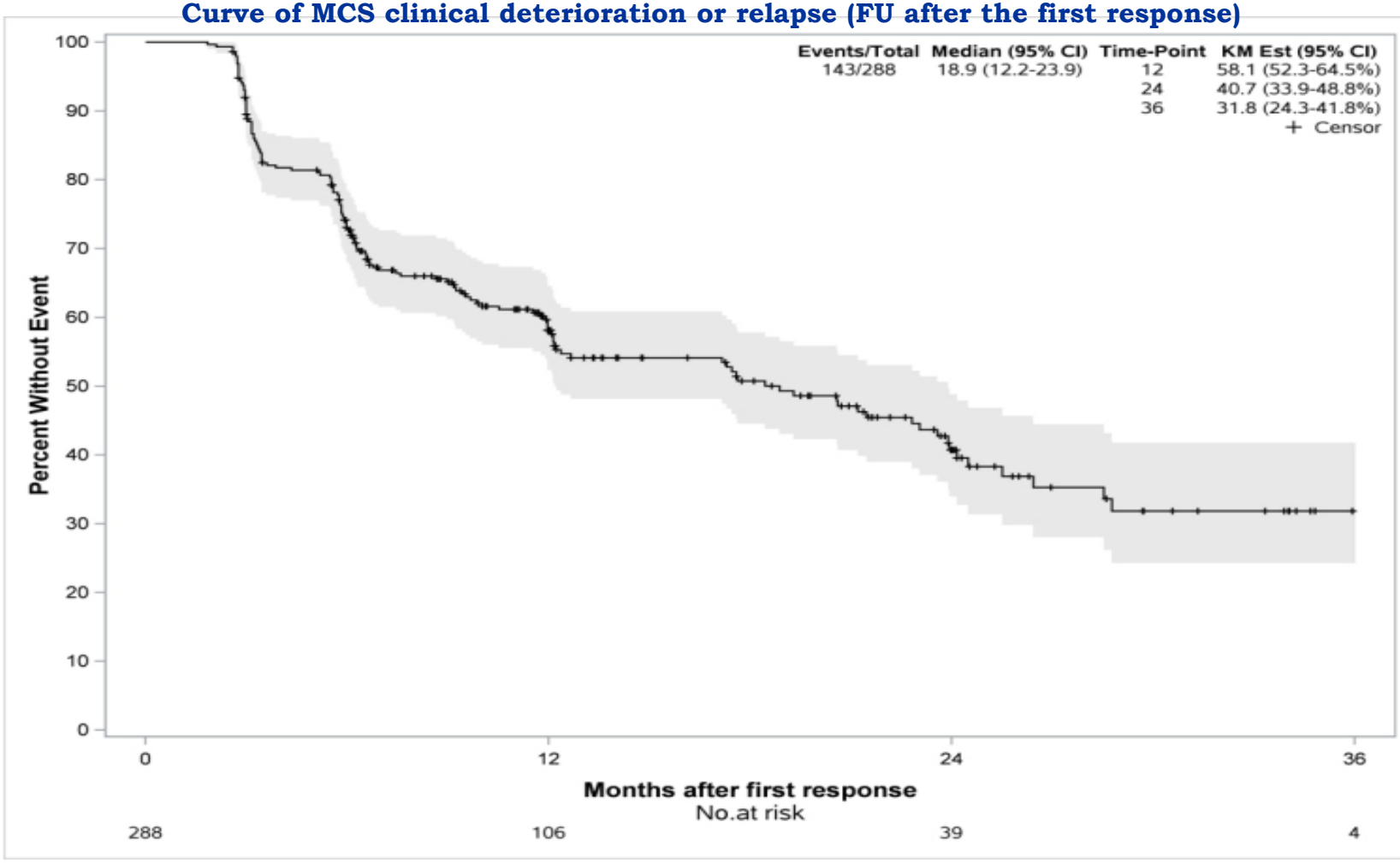
FCR persistent only in 21.5%

Clinical relapse in 11% (transient in 70%)

NR in 12%

Symptoms that persisted more frequently: arthralgia (45%) fatigue (41%) neuropathy (38%) and sicca syndrome (37%)

Curve of MCS clinical deterioration or relapse (FU after the first response)



Flares of CV after Vaccination Against SARS-CoV-2

Visentini M, Gragnani L, Santini SA, Urraro T, Villa A, Monti M, Palladino A, Petraccia L, La Gualana F, Lorini S, Marri S, Madia F, Stefanini S, Basili S, Fiorilli M, Ferri C, Zignego AL, Casato M

- Flares in 6/63 (9.5%) CV patients: did not endanger patients and subsided spontaneously thus reassuring the safety of SARS-CoV-2 vaccination in patients with MC
- Anti-SARS-CoV-2 IgG responses: seronegative 11.6% RTX-free and 71% RTX treated patients (p=0.002)
- Seronegativity was more frequent (p=0.04) among patients with EMC than in SVR HCV-MC, suggesting lower immune dysregulation due to reversion of B cell abnormalities after clearance of infection

These observations encourage administering vaccine booster to patients with MC and postponing vaccination of RTX-treated patients after B cell repopulation

Patient	Age (years)/ sex	MC type	SVR (months)	Last active symptoms and RTX before vaccination (months)		Vaccine	Symptoms after first dose	Symptoms after second dose
				Symptoms	RTX			
1	70/male	EMC	N/A	P (40)	N/T	AstraZeneca	Diffuse P (day 3)	Second dose refused
2	41/female	EMC	N/A	P (20)	20	Pfizer	None	Diffuse P (day 1)
3	76/female	EMC	N/A	P (27)	N/T	Pfizer	None	Diffuse P (day 5)
4	57/female	HCV-MC	67	PN (42)	N/T	Pfizer	None	Moderate P, PN (day 10)
5	66/female	HCV-MC	62	P, PN (48)	N/T	Pfizer	None	Moderate P, PN (day 7)
6	63/female	HCV-MC	30	P, PN (26)	N/T	Pfizer	None	Moderate P (day 7)

BMJ Journals
Annals of the Rheumatic Diseases

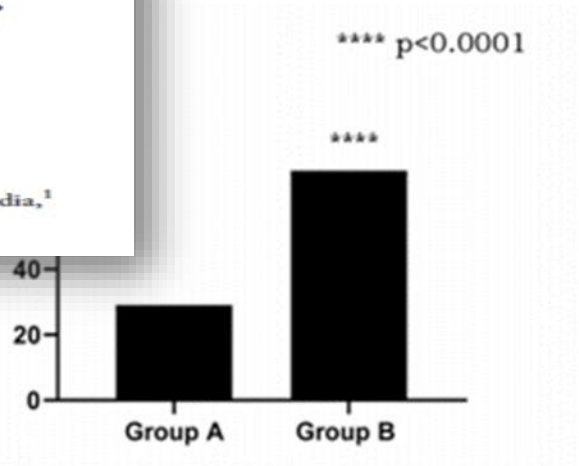
HEPATOLOGY
VIRAL HEPATITIS | HEPATOLOGY, VOL. 74, NO. 3, 2021

Hematological and Genetic Markers in the Rational Approach to Patients With HCV Sustained Virological Response With or Without Persisting Cryoglobulinemic Vasculitis

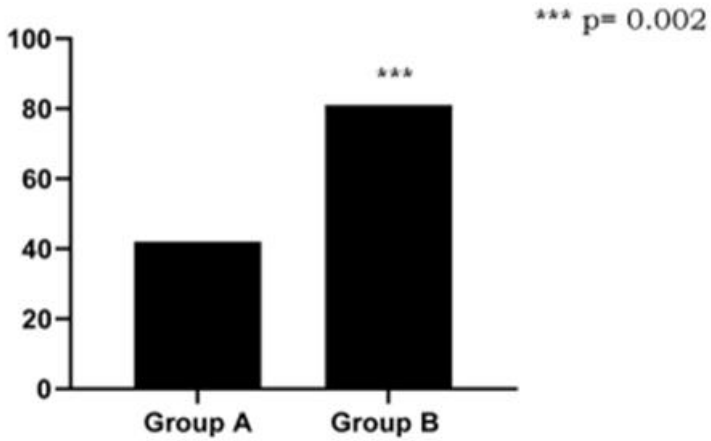
Laura Gragnani ,[1] Serena Lorini,[1] Silvia Marri,[1] Umberto Basile,[2] Veronica Santarlasci,[1,3] Monica Monti,[1] Francesco Madia,[1] Luisa Petraccia,[1] Cristina Stasi,[1] Niccolò Marello,[1] Cecilia Napodano,[4] Francesco Annunziato,[3] and Anna Linda Zignego[1]

S

sence of at least One Clonality Marker [MBL, T(14:18), FLC]



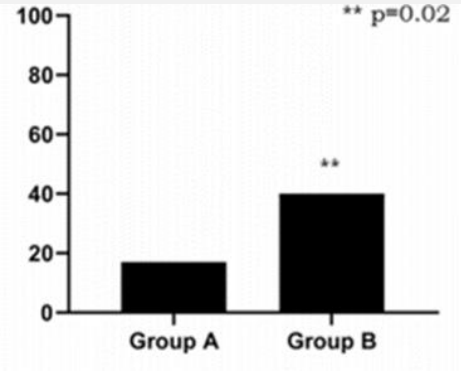
POST-DAAs end of F-U

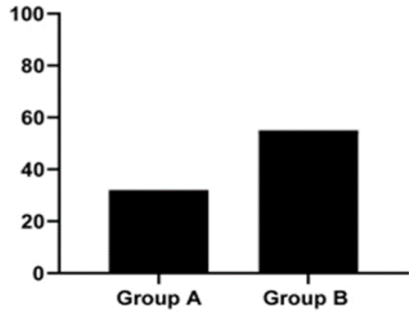


PRE-DAAs

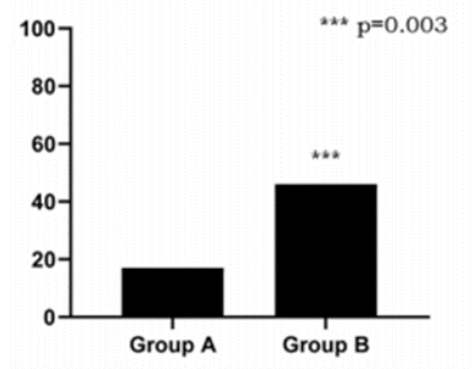
Group A Group B

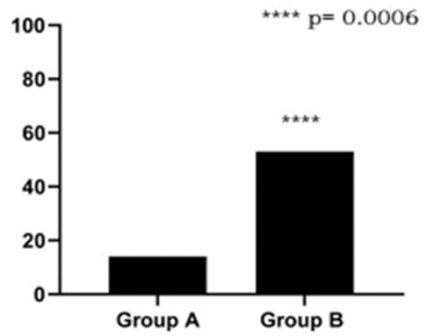
POST-DAAs EOFU **T(14;18)** PRE-DAAs Basis





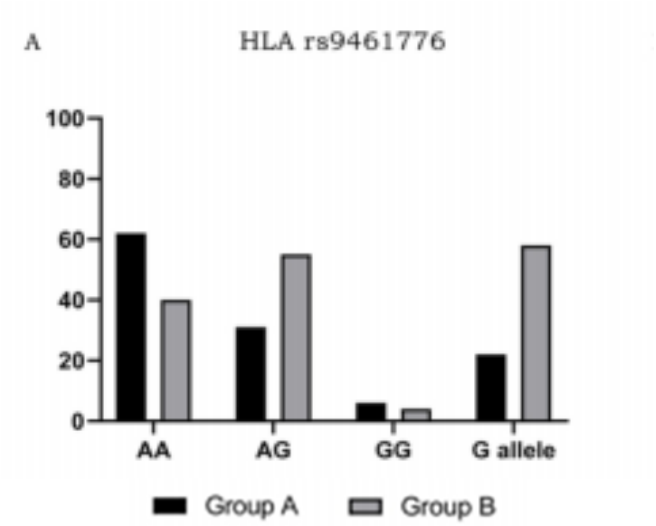
POST-DAAs EOFU **serum FLC k/λ ratio** PRE-DAAs Basis





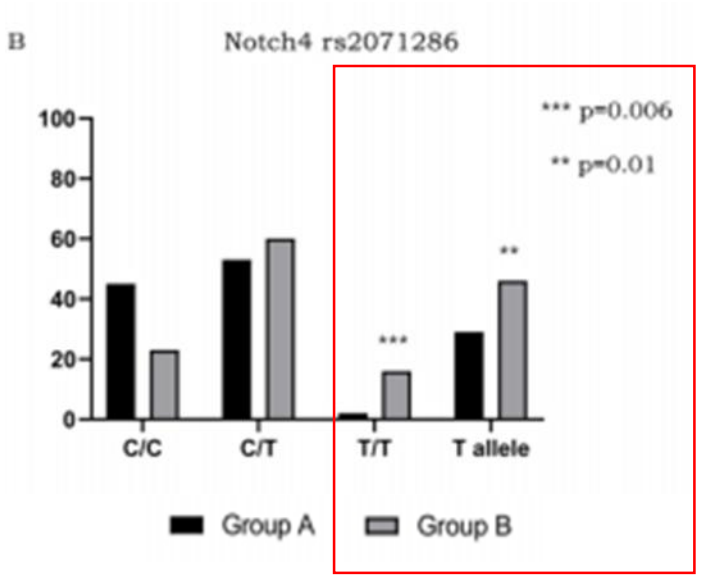
Gragnani et al. Hepatology 2021

Genetic marker analysis



Distribution of polymorphic variant of the HLA class II rs9461776.

The heterozygous genotype A/G and **G minor allele** were more frequent in Group B than in Group A (respectively 56% vs 31% and 33% vs 22%). The homozygous minor genotype G/G showed similar frequency between the two groups (6% in Group A vs 4% in Group B)



Distribution of polymorphic variant of the Notch4 rs2071286.

Significant association between rs2071286 SNPs and Group B patients with the dominant and recessive model of penetrance (C/C vs C/T+T/T for the dominant model of penetrance: p=0.04 OR=0.37, 95% CI:0,1434-0,9158; for the recessive model of penetrance: T/T vs C/T+C/C p=0.02 OR=9.33 95% CI: 1,099-79,28)

Homozygous haplotype T/T: 2% Group A vs 16% Group B p=0.006. T minor allele frequency: 29% Group A vs. 47% Group B (p=0.01 OR=2.17 95% CI=1.18-3.9)

Gragnani et al. Hepatology 2021

Predictors of long-term cryoglobulinemic vasculitis outcomes after HCV eradication with direct-acting antivirals in the real-life

Laura Gragnani [a], Serena Lorini [a], Silvia Marri [a], Caterina Vacchi [b], Francesco Madia [a], Monica Monti [a], Clodoveo Ferri [c,*,1], Anna Linda Zignego [a,1]

Autoimmunity Reviews 21

- 109 consecutively CV patients treated with DAAs
- The mean post-therapy follow-up was 137 weeks (range: 72–290 weeks)
- At the EOFU, clinical and immunological response was available for 108/109 patients, all SVR, as follows: 17% FCR, 12% CR, 19% PR, and 52% NR

The newly created scores, CV- and Global Severity Index

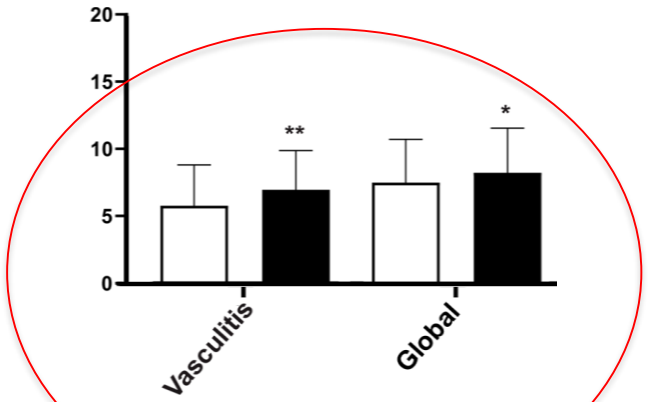
SEVERITY INDEX ASSESSMENT

	VASCULITIS	GLOBAL
Purpura	3	3
Neuropathy	1 sensory, 2 motor-sensory, 3 paresis	1 sensory, 2 motor-sensory, 3 paresis
Arthritis	1	1
Sicca syndrome	1	1
Nephropathy	1 proteinuria, 2 proteinuria + high creatinine ratio, 3 kidney failure	1 proteinuria, 2 proteinuria + high creatinine ratio, 3 kidney failure
Lymphoma	3	3
Hematologic alterations	2 leukopenia, 3 pancytopenia	1 thrombocytopenia, 2 leukopenia, 3 pancytopenia
Abdominal vasculitis	3	3
Liver	-	1 F0-F1, 2 F2-F3, 3 F4
Other symptoms/signs*	1 (1 symptom/sign), 2 (2 symptoms/signs), 3 (all of them)	1 (1 symptom/sign), 2 (2 symptoms/signs), 3 (all of them)
Highest score	**20**	**23**

Analysis on population stratified on the clinical response

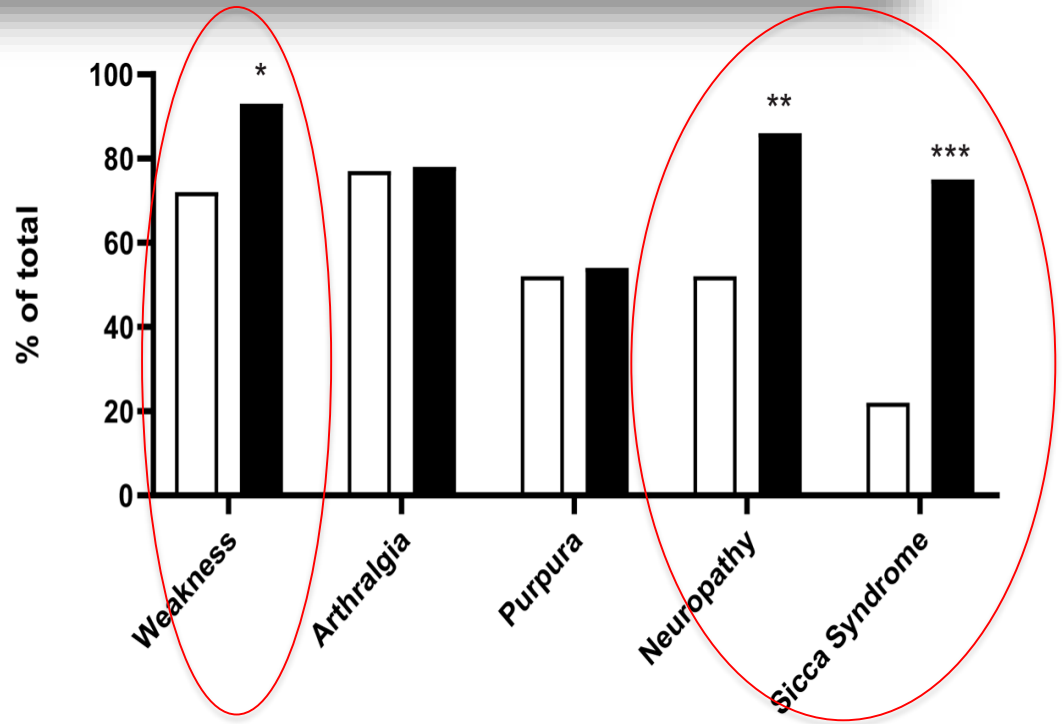
- We proposed **two novel indexes assessing the severity of CV**, taking into account either the presence of only extrahepatic manifestations or both hepatic and extrahepatic HCV disorders.
- Interestingly, **both Severity Indexes were correlated to the CV clinical response**
- Together with some **baseline symptoms (neuropathy, weakness and sicca syndrome),** the two newly created scores, **Vasculitis and Global Severity Index**, emerged as reliable and standardized **tools to predict CV outcome** before antiviral therapy.

* p ≤0.01 ** p ≤0.005 *** p ≤0.0001.



* p ≤0.01 ** p ≤0.005 *** p ≤0.0001.

VASCULITIS and GLOBAL SEVERITY INDEX



BASELINE SYMPTOMS

Gragnani et al. Autoimmun Rev 2021

Factors associated with FCR (*restitution ad integrum*) without clinical deterioration or relapse

PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

		Univariate analysis N=369		Multivariate analysis N=278	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Age (years)		0.96 (0.94-0.98)	<.0001	0.96 (0.94-0.99)	0.002
Sex	Male	1			
	Female	0.42 (0.25-0.69)	0.001		
Purpura	No	1			
	Yes	0.32 (0.14-0.74)	0.008		
Asthenia	No	1			
	Yes	0.41 (0.25-0.68)	0.001	0.53 (0.26-1.10)	0.088
Arthralgia	No	1			
	Yes	0.44 (0.27-0.72)	0.001		
Neuropathy	No	1			
	Yes	0.4 (0.23-0.69)	0.001	0.4 (0.18-0.87)	0.022
Renal involvement	No	1			
	Yes	0.75 (0.37-1.53)	0.434		

		Univariate analysis N=369		Multivariate analysis N=278	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Renal involvement	No	1			
	Yes	0.75 (0.37-1.53)	0.434		
Xerostomia/Xerophthalmia	No	1			
	Yes	0.6 (0.36-1.00)	0.051		
Raynaud	No	1			
	Yes	0.54 (0.25-1.19)	0.128		
Ulcers		1.04 (0.25-4.24)	0.960		
Pretreatment Cryocrit		0.81 (0.67-0.99)	0.041	0.81 (0.66-0.98)	0.03
Pretreatment		1 (0.99-1)	0.202		
Rheumatoid Factor					
Pretreatment C4		1.2 (0.97-1.48)	0.090		

HEPATOLOGY AASLD

Kondili et al, 2021

Factors Associated with Clinical Deterioration/Relapse After Clinical Response in CV Patients* (no. 288)

PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

HEPATOLOGY AASLD *Kondili et al, 2021*

		Univariate analysis N=288		Multivariate analysis N=94	
Variable		HR (CI 95%)	p value	HR (CI 95%)	p value
Age (years)		1.01 (1.00-1.02)	0.178		
Sex	Male	1			
	Female	1.01 (0.71-1.44)	0.937		
Purpura	No	1			
	Yes	0.67 (0.45-1.01)	0.055	0.75 (0.41-1.37)	0.349
Asthenia	No	1			
	Yes	1.08 (0.71-1.64)	0.730		
Arthralgia	No	1			
	Yes	0.89 (0.63-1.26)	0.507		
Neuropathy	No	1			
	Yes	1.34 (0.95-1.88)	0.092	1.38 (0.74-2.56)	0.313
Renal involvement	No	1			
	Yes	0.91 (0.58-1.41)	0.672		

	Univariate analysis N=288		Multivariate analysis N=94	
Variable	HR (CI 95%)	p value	HR (CI 95%)	p value
Xerostomia Xerophthalmia	1			
	..41 (1.01-1.99)	0.047	0.84 (0.52-1.70)	0.841
Raynaud	1			
	.87 (0.57-1.32)	0.512		
Ulcer	1			
	.43 (0.11-1.72)	0.232		
Pretreatment Cryocrit	.99 (0.94-1.03)	0.514		
Pretreatment Rheumatoid Factor	1 (1.00-1.001)	0.017	1 (1.00-1.001)	0.021
Pretreatment C4	.99 (0.89-1.09)	0.786		
Rituximab	1			
	.65 (0.29-1.48)	0.303		

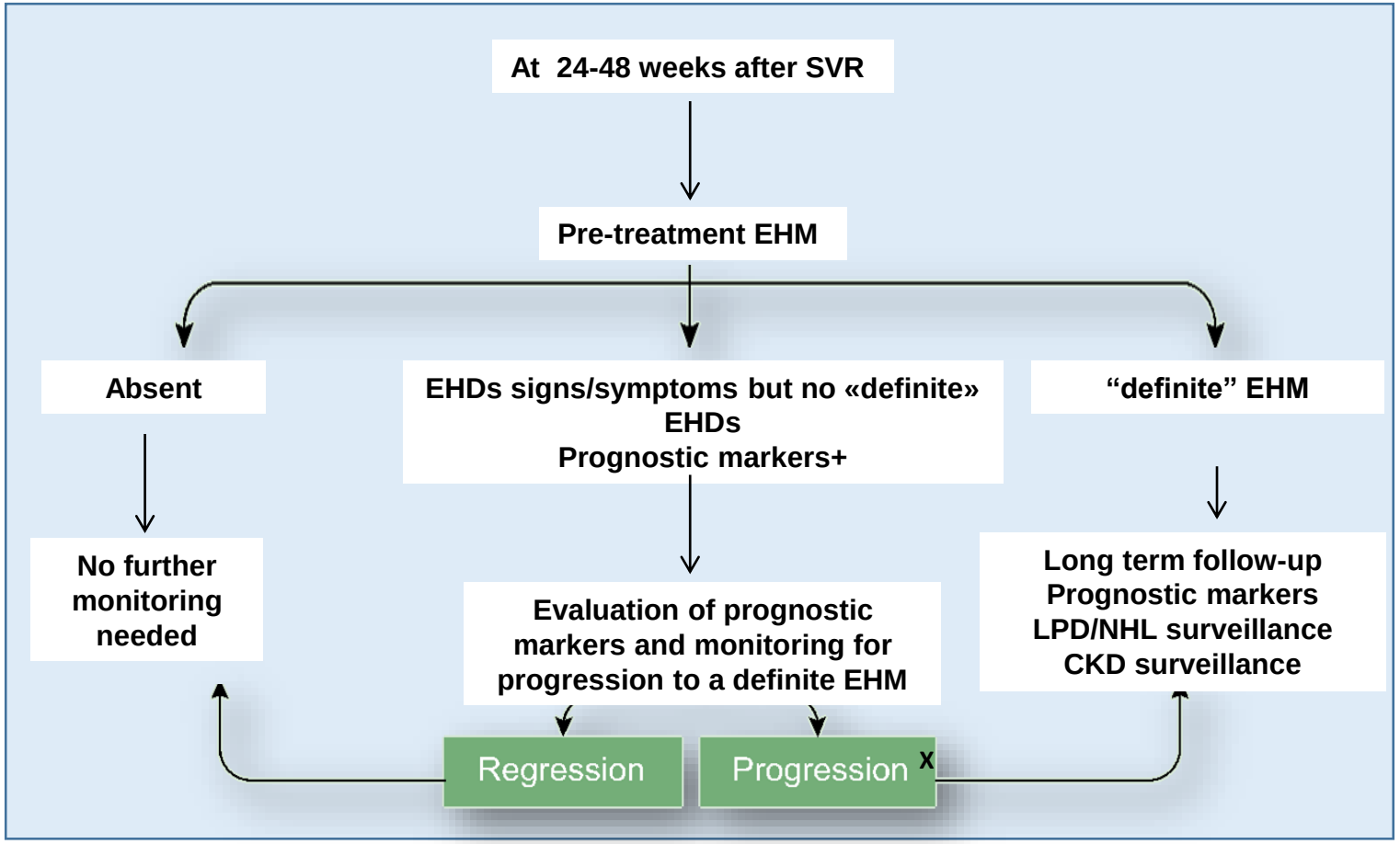
CONCLUSIONS

In conclusion, the prospective analysis of DAA-treated cryoglobulinemic patients enrolled consecutively in a nationwide cohort, including the large majority of hepatological Italian centers, was able to:

- -confirm that after SVR most CV patients reach a clinical response that increases over time
- -clearly show that the clinical response frequently fluctuates. Indeed, the clinical manifestation pattern may change over and reappear, either persistently or transiently
- -the combination of patients who maintain symptoms and those in whom symptoms reappear implies a careful patient assessment and post-HCV eradication monitoring

In this light, the accurate evaluation of both clinical and laboratory factors that represent prognostic indexes will aid in predicting different clinical evolutions. This will permit us to tailor the frequency and quality of follow-up appointments, as recommended for HCV-related liver damage which will assist in the selection of the best therapeutic approach following HCV eradication.

Taylored Post AVT Follow-Up of HCV-MC Patients



*Consider RTX treatment in persisting B-cell clonality

Prognostic Factors:

- Laboratory: Clonality Biomarkers (FLC k/Lambda ratio, T(14;18), MBL); Genetic Biomarkers (Notch4 polymorphism); high cryocrit; high RF values
- Demographical/Clinical: Age; Neuropathy; Weakness; SS; (CKD)
- CV and Global Severity Indexes