X Workshop Nazionale

Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI

Firenze, 13-14 gennaio 2020

Centro Congressi Hotel Londra

Follow-up del Paziente con Patologie Extraepatiche

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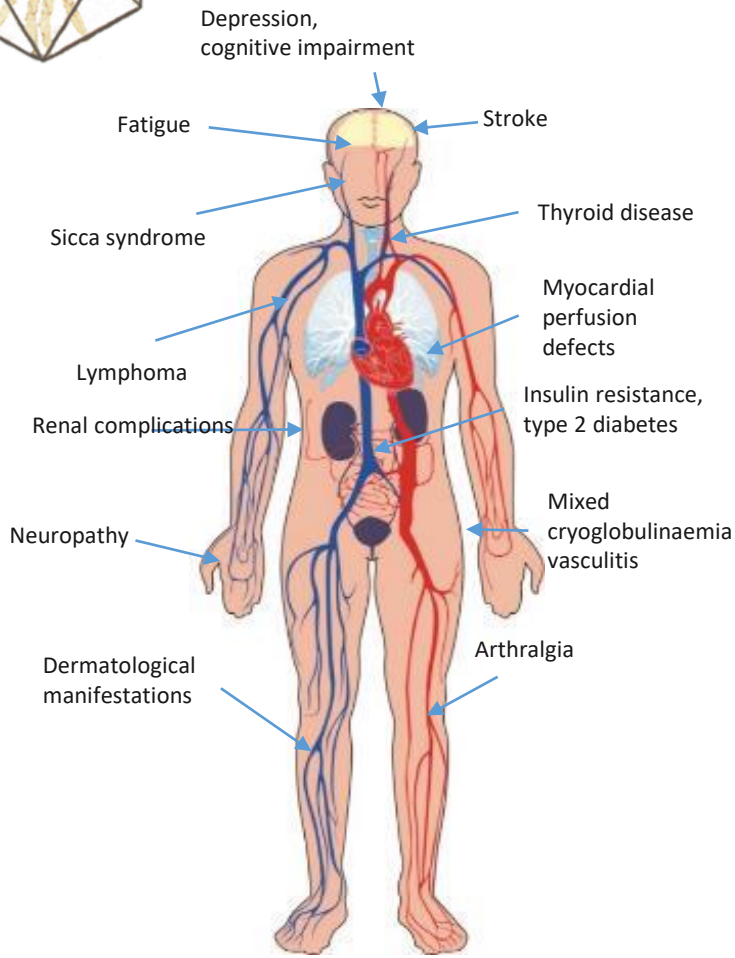
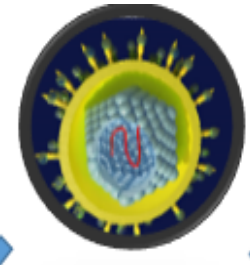
Centro di Ricerca ed Innovazione Aziendale CRIA-MASVE AOU Careggi

HCV infection and associated diseases: "morbidities" vs "comorbidities"





Morbidities

Hepatic

Acute/chronic hepatitis
HCV-related Steatosis (GT3)
Cirrhosis
HCC (in part)

Extrahepatic

Autoimmune and/or lymphoproliferative diseases (benign –MC- or malignant –NHL-)

Comorbidities (?)

e.g,
Cardiovascular
Type 2 Diabetes
Psychiatric
Renal (non MC)
Tyreopaties
Tumors (no HCC or LNH)
(Other…)

ACCORDING TO THE META-ANALYSIS OF >100 STUDIES HCV PATIENTS HAVE:

- -23% increased risk of developing a progressive and/or end-stage kidney disease
- -23% increased risk of type 2 diabetes
- -20% increased risk of cardiovascular disease
- -35% increased risk of cerebrovascular disease
- -2 times greater risk of developing lichen planus, SS, RA-like arthritis and depression
- -8 times higher risk of developing porphyria cutanea tarda…

Younossi et al. 2016; Petta et al. 2016

- The analysis of mortality rates in large cohorts confirmed the association of HCV with several EHDs including cardiovascular, neurologic, metabolic or renal diseases and tumors
- Viral eradication significantly reduced the rate of extra-hepatic deaths

All-cause mortality amongst HCV RNA+ patients was higher for those who developed a non-liver-related disease

Hsu YC, *et al.* Hepatology 2014; Kawamura Y, *et al.* Am J Med 2007; Adinolfi LE, *et al.* WJG 2014

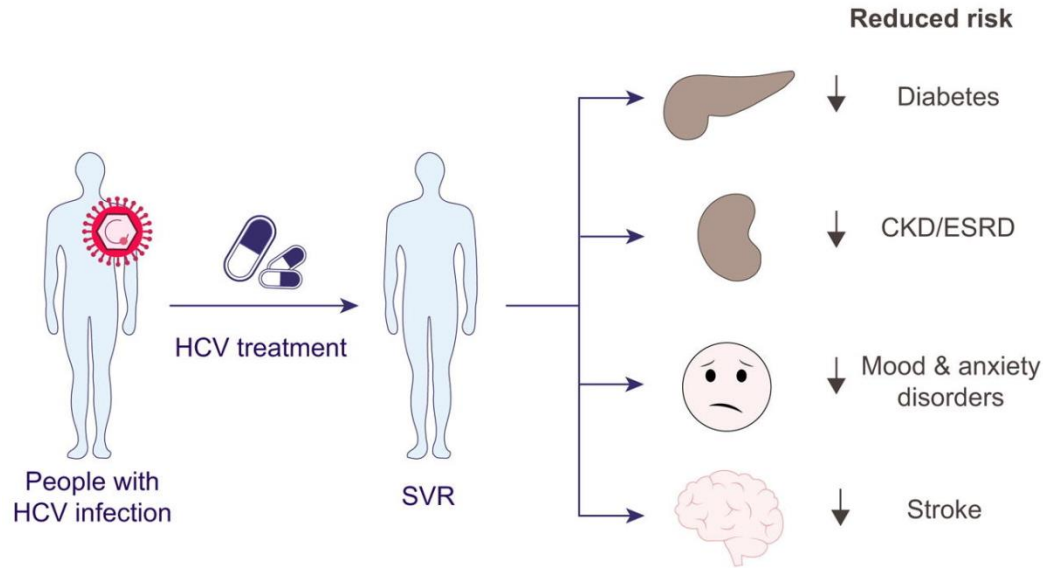
Sustained virologic response from interferon-based Hepatitis C treatment is associated with reduced extrahepatic manifestations risk

Rossi C *et al* Journal of Hepatology
Volume 71, Issue 6, December 2019, Pages 1116-1125

Longitudinal cohort study using data from the British Columbia Hepatitis Testers Cohort (~1.3 million individuals screened for HCV): 10 264 HCV+ patients treated with IFN between 1999 and 2014; 6 023 SVR (59%)

EHM risk was significantly reduced among patients with SVR for:

- type 2 diabetes mellitus
(asHR 0.65; 95% CI 0.55–0.77)
- chronic kidney disease or end-stage renal disease
(asHR 0.53; 95% CI 0.43–0.65)
- ischemic or hemorrhagic stroke
(asHR 0.73; 95% CI 0.49–1.09)
- mood and anxiety disorders
(asHR 0.82; 95% CI 0.71–0.95)



SVR was associated with a reduction in the risk of several EHMs. Increased uptake of antiviral therapy may reduce the growing burden of EHMs in this population.

Sustained virologic response from interferon-based Hepatitis C treatment is associated with reduced extrahepatic manifestations risk

Rossi C *et al*

Journal of Hepatology

Volume 71, Issue 6, December 2019, Pages 1116-1125

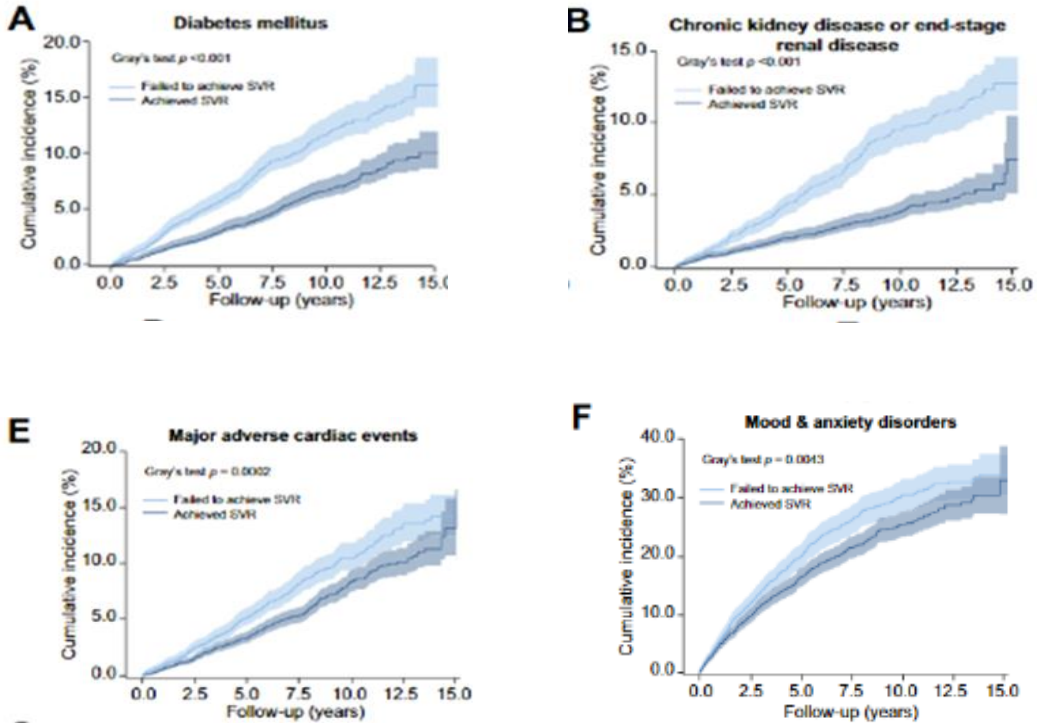


Table 2. Effect of SVR on incident extrahepatic manifestations using proportional hazards model accounting for competing mortality risk, according to covariate adjustment.[†]

	Adjusted subdistribution hazard ratios (95% CI)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Diabetes	0.60 (0.51–0.70)	0.60 (0.51–0.70)	0.58 (0.50–0.68)	0.66 (0.56–0.78)	0.65 (0.55–0.77)
Chronic kidney disease or end-stage renal disease	0.46 (0.38–0.56)	0.46 (0.38–0.56)	0.48 (0.39–0.58)	0.50 (0.41–0.62)	0.53 (0.43–0.65)
Ischemic or hemorrhagic stroke	0.64 (0.45–0.92)	0.64 (0.44–0.93)	0.68 (0.47–0.98)	0.71 (0.48–1.04)	0.73 (0.49–1.09)
Ischemic heart disease	1.08 (0.92–1.28)	1.10 (0.93–1.30)	1.08 (0.92–1.28)	1.20 (1.01–1.43)	1.23 (1.03–1.47)
Major adverse cardiac events	0.83 (0.71–0.98)	0.85 (0.72–0.99)	0.85 (0.73–1.0)	0.90 (0.76–1.06)	0.93 (0.79–1.11)
Mood and anxiety disorders	0.78 (0.68–0.89)	0.81 (0.71–0.93)	0.78 (0.68–0.90)	0.80 (0.69–0.92)	0.82 (0.71–0.95)
Rheumatoid arthritis	1.11 (0.74–1.66)	1.11 (0.74–1.66)	1.07 (0.71–1.59)	1.14 (0.76–1.71)	1.09 (0.73–1.64)

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

424 HCV+ patients consecutively recruited from July 2003 to July 2010 at the MASVE Center for standard anti-HCV treatment with pegIFN + RBV

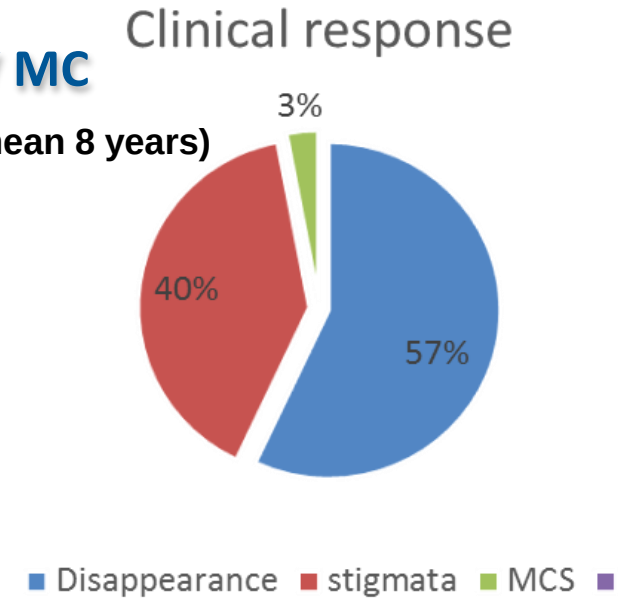
- 121 HCV+ with MCS
- 158 HCV+ without MCS or MC
- 132 HCV + with MC without MCS

[13 patients of uncertain classification: excluded]

Long-term outcome of HCV MC

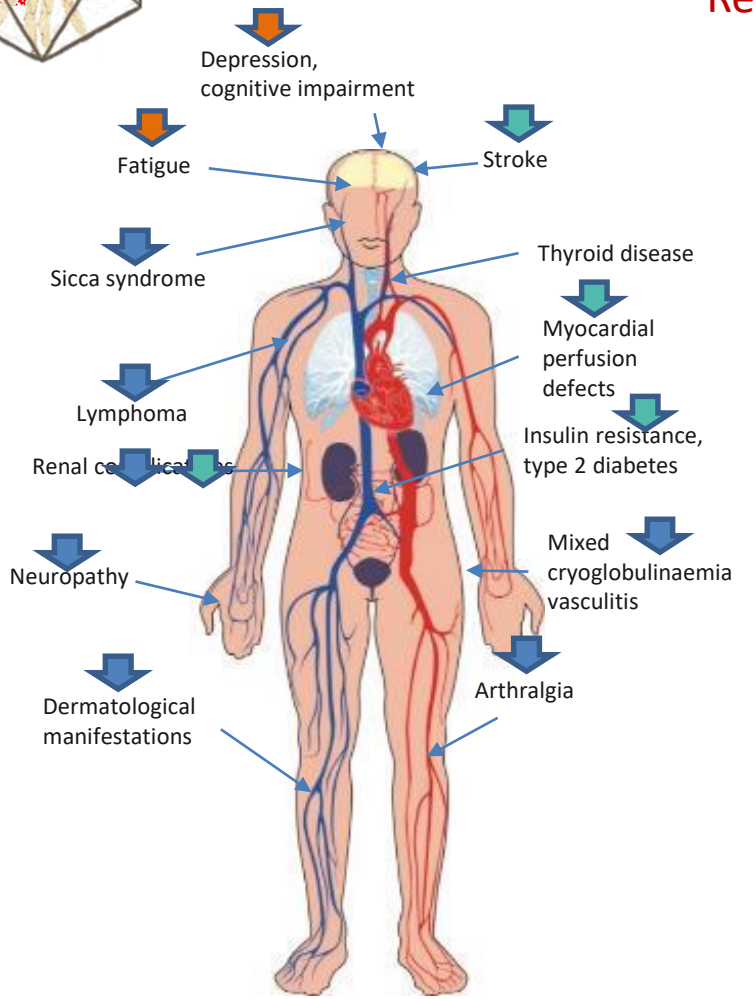
Post-treatment follow-up: 30 to 120 months (mean 8 years)

- Disappearance of MC symptoms/signs in the majority (57%) of SVR patients
- Persisting isolated MCS stigmata (signs and/or symptoms) in 40% of SVR patients
- Persisting MC syndrome in 3% of SVR patients
- No evolution to lymphoma in SVR patients
- No MCS remission in non SVR patients



Hepatology, Gragnani et al, 2015

Extrahepatic benefits of HCV eradication: Summary



Reduced all-cause mortality

Autoimmune/B-cell LPDs=

- resolution of MC manifestations
- regression/remission of HCV-associated lymphoma

Cardiovascular diseases/Diabetes and insulin resistance=

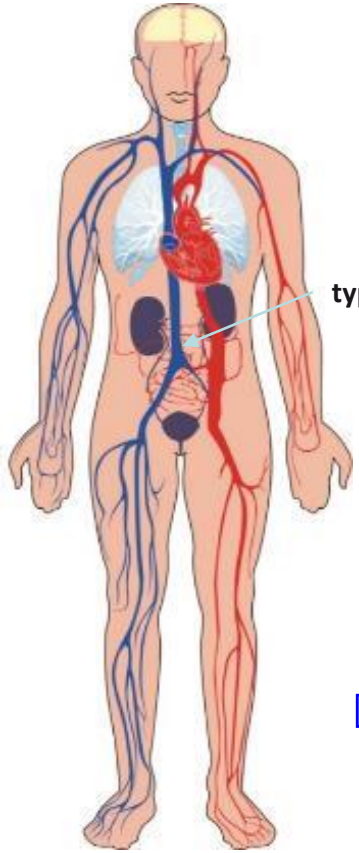
- improvement in myocardial perfusion defects
- reduced incidence of stroke
- reduced renal and cardiovascular outcomes in diabetics
- reduced risk of insulin resistance
- reduced risk of type 2 diabetes

Cognitive and functional=

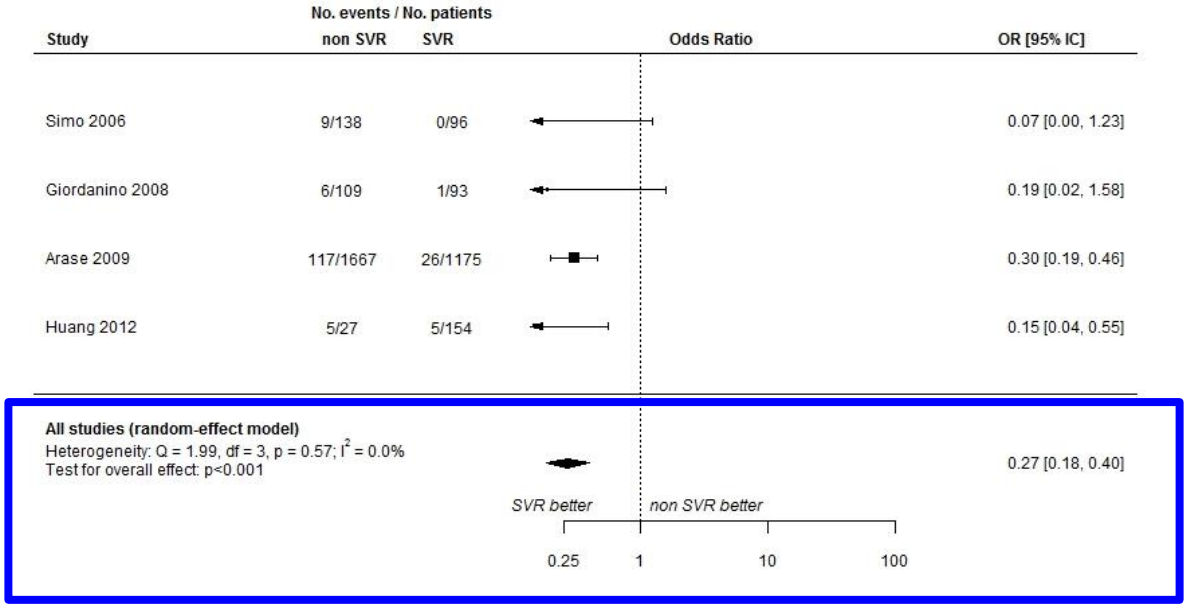
- improved cognitive performance
- reduction in fatigue
- gains in quality of life

Impact of SVR on diabetes in HCV patients, a meta-analysis

Outcome: Incidence of *de novo* diabetes



type 2 diabetes



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

HOMA-IR <	
HOMA-IR 2,4 - 4	Insulin-resistance
HOMA-IR > 4	Mild type II diabetes
HOMA-IR > 6	Type II diabetes

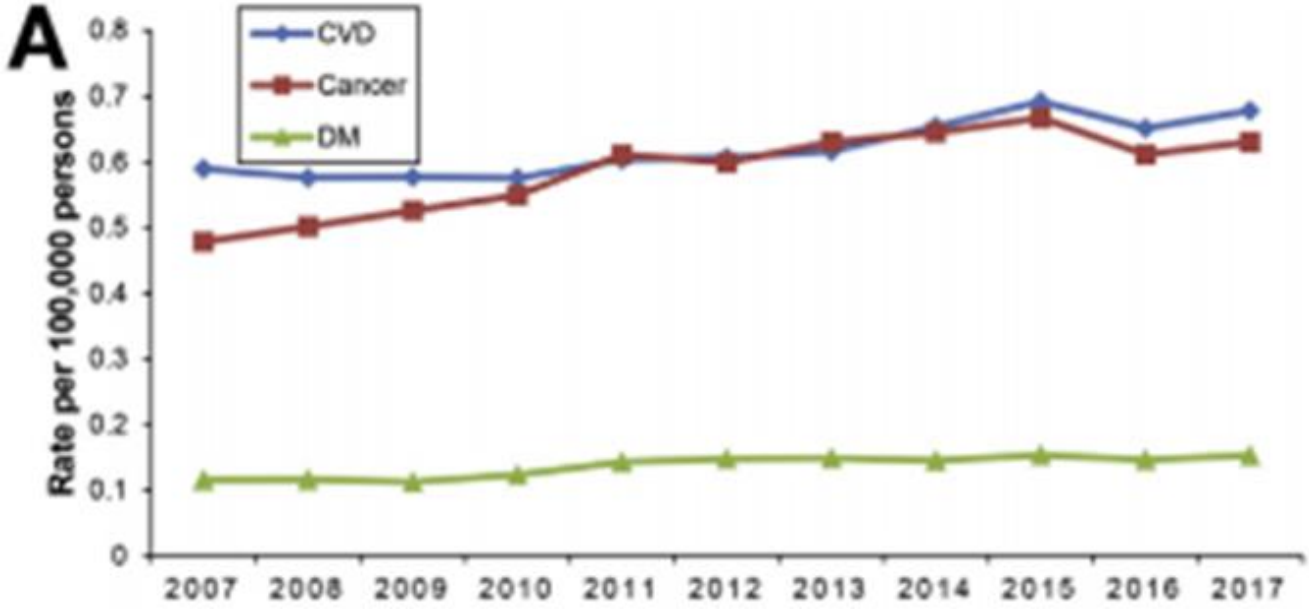
Cacoub P et al, GUT 2018

Trends in Mortality From Extrahepatic Complications in Patients With Chronic Liver Disease, From 2007 Through 2017

Kim et al Gastroenterology 2019;157:1055–1066

- 9378 adults aged 17–59 years utilizing the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File
- HCV status assessed from 1988 to 1994: mortality follow-up through 2006

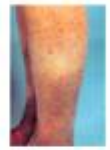
Age-standardized mortality due to chronic HCV infection
2007-2017



Kim et al, Gastroenterology 2019

MIXED CRYOGLOBULINEMIA

HCV induces monoclonal expansion of B cells producing rheumatoid factor that forms cryoprecipitable immune complexes causing small vessel vasculitis.



Purpura >90%

Neuropathy ≈80%

Glomerulonephritis ≈30%

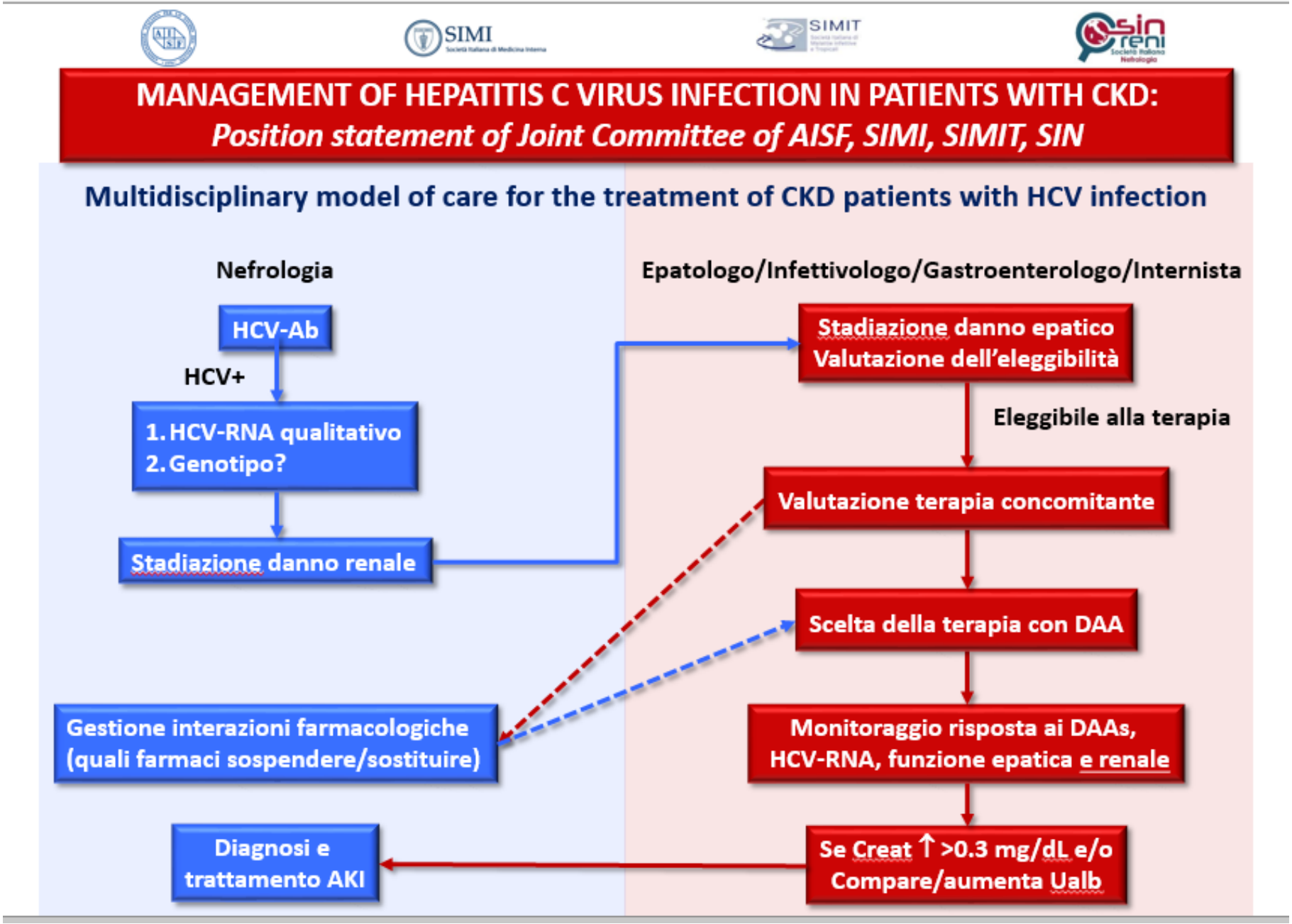
Skin ulcers ≈15%

1

1

5-10% of patients develop B cell lymphoma over time

Most (70–90%) MC patients are HCV+ and HCV-patients are CGs+ (40–60%), while 5–30% of CGs+ have symptomatic MC



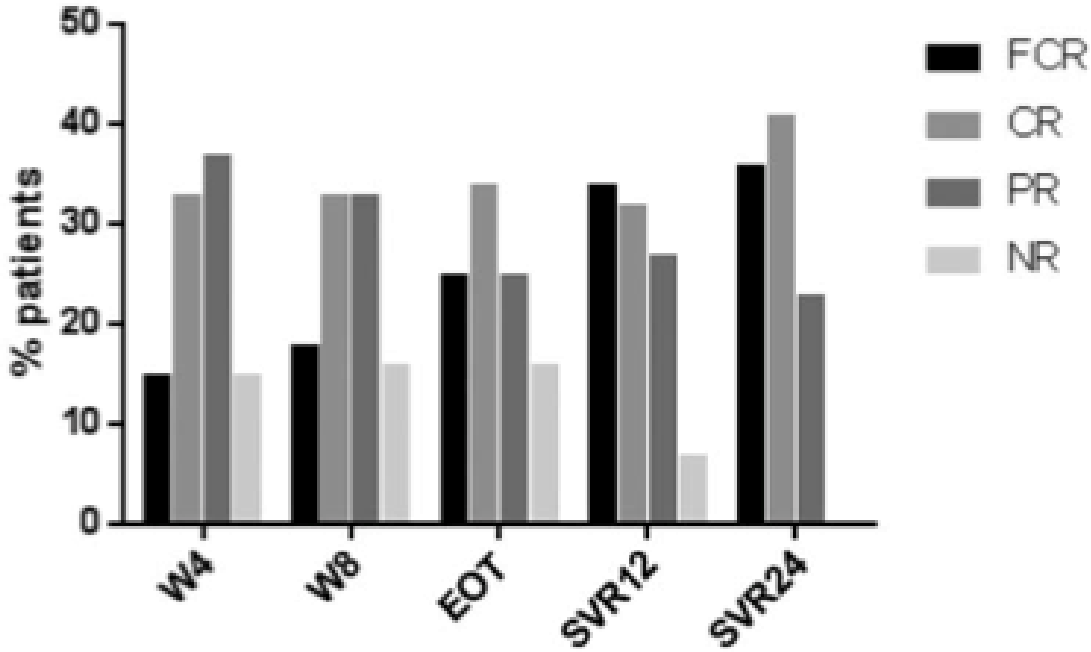
Minutolo et al, 2018: Dig Liver Dis, Intern Emerg Med, J Nephrol; 2019: Infection

Prospective Study of Guideline-Tailored Therapy With Direct-Acting Antivirals for Hepatitis C Virus-Associated Mixed Cryoglobulinemia

Risposta completa
Miglioramento di tutte le manifestazioni cliniche basali

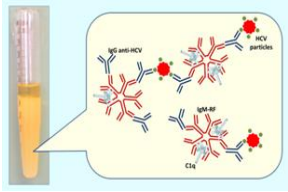
Risposta parziale
Miglioramento almeno del 50% delle manifestazioni cliniche basali

Non-risposta
Restanti situazioni



Full complete responders
Scomparsa di tutte le manifestazioni cliniche basali

Gragnani et al, Hepatology, 2016



Mixed Cryoglobulinemia

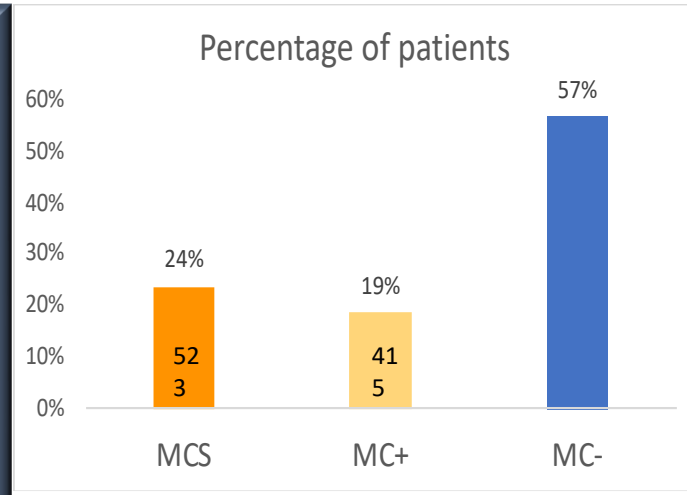
PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

- *The presence of MC was not tested in 76% of cases in spite of its clinical and therapeutical importance*

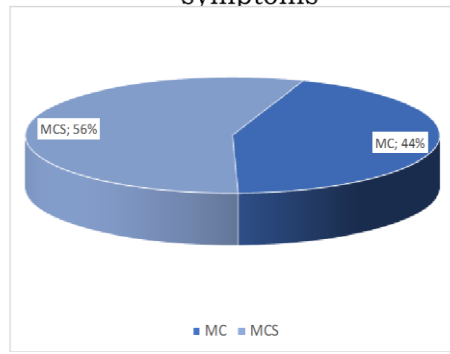
Total evaluated HCV+ patients: 2191

- 523 MC had typical Symptoms and were considered as confirmed MCS
- 415 patients had asymptomatic crioglobulinemia (MC+)
- 1253 patients tested negative for MC (MC-)

Cryoglobulinemic patients: 938



Percentage of cryoglobulinemic patients with (MCS) or without (MC) symptoms



Antiviral Therapy in patients with MCS: PRELIMINARY RESULTS

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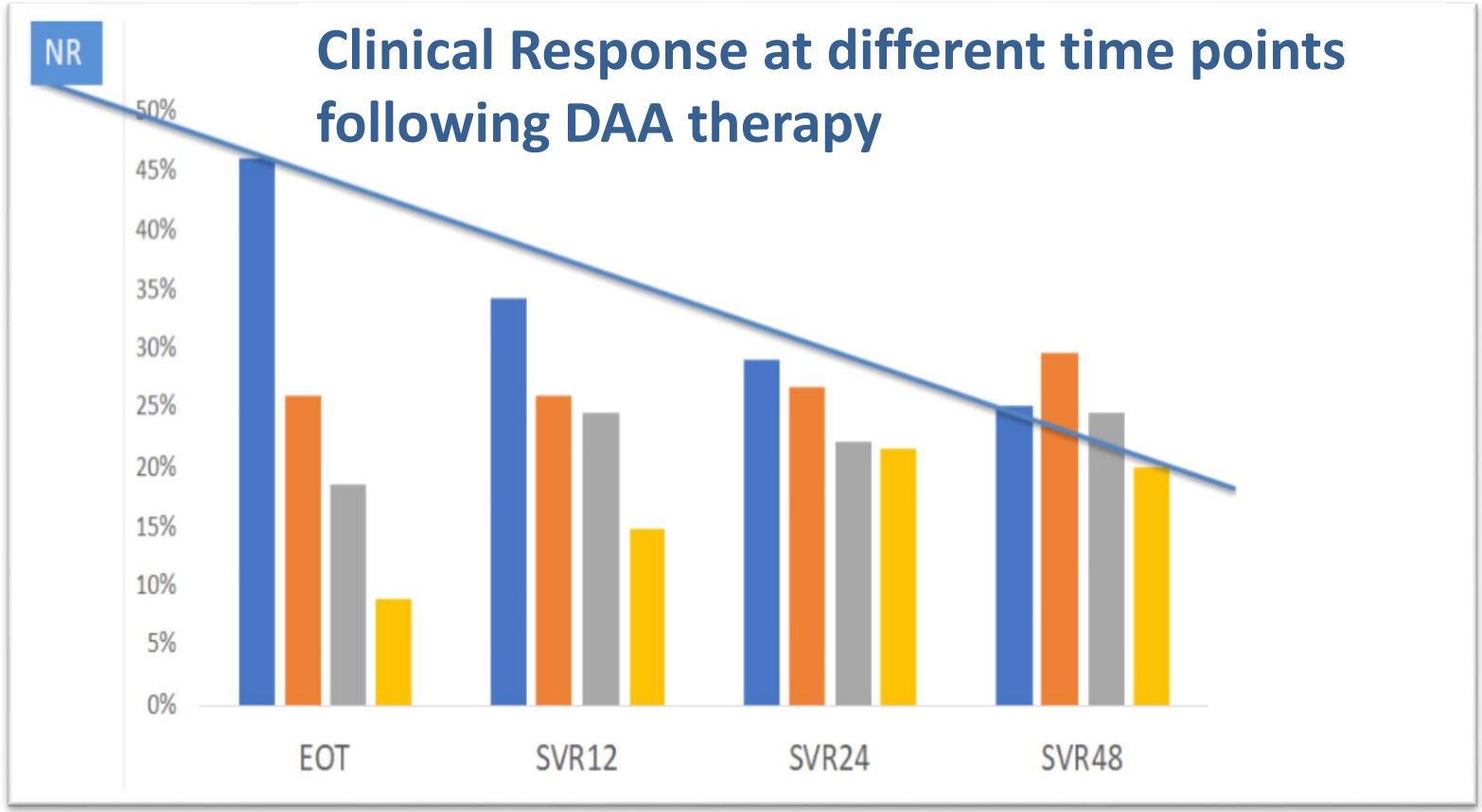
Virological Response: 97% and 96% in MC and MCS, respectively
Clinical Response: about 80% including FCR, CR, PR, NR

Full complete response (FCR)
Disappearance of all Symptoms
(*restitutio ad integrum*)

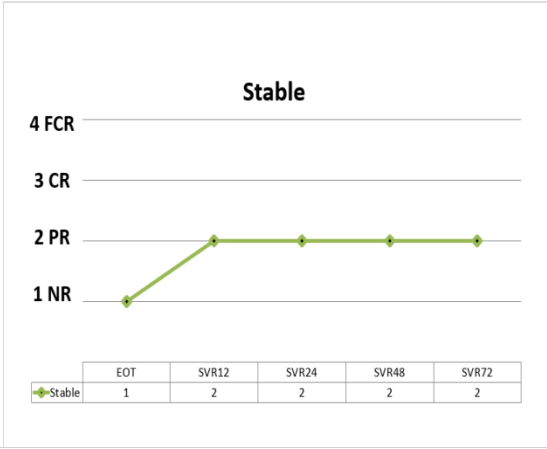
Complete response (CR)
Improvement of all Symptoms

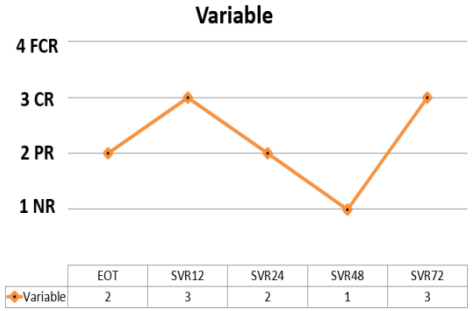
Partial response (PR)
nprovement of more than 50% of symptoms

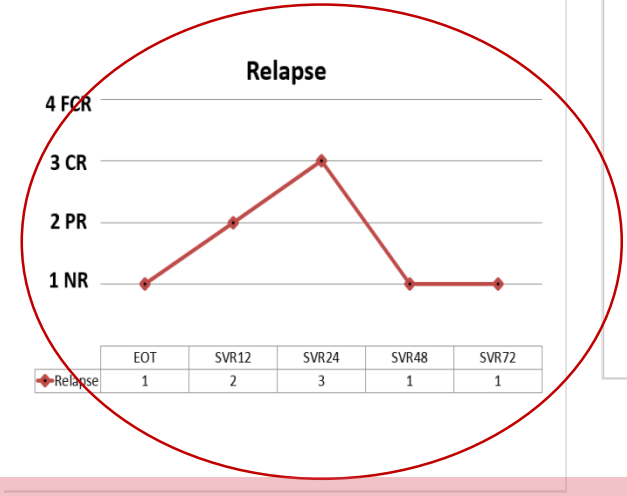
Non-response (NR)
Remaining conditions

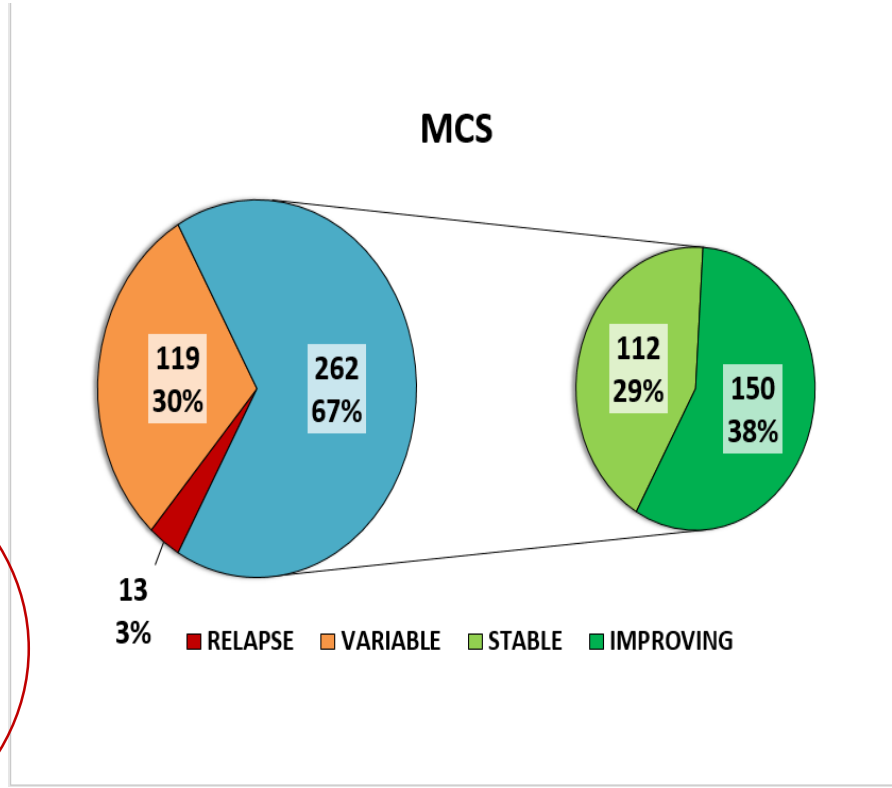


Post Treatment Symptoms in SVR patients= Observed patterns





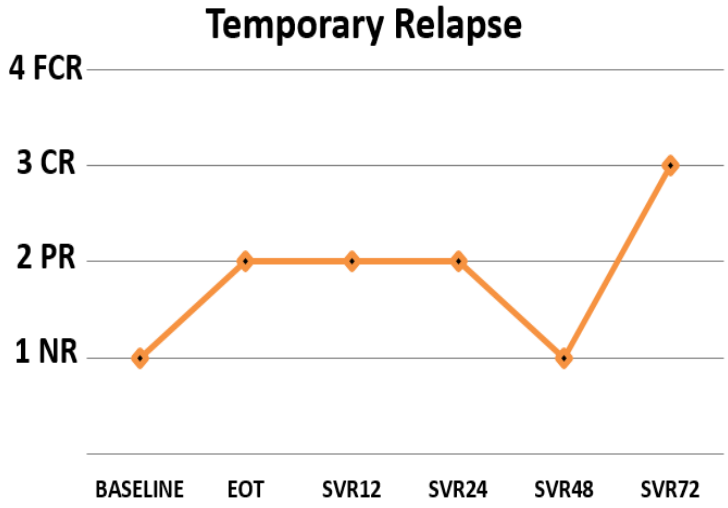


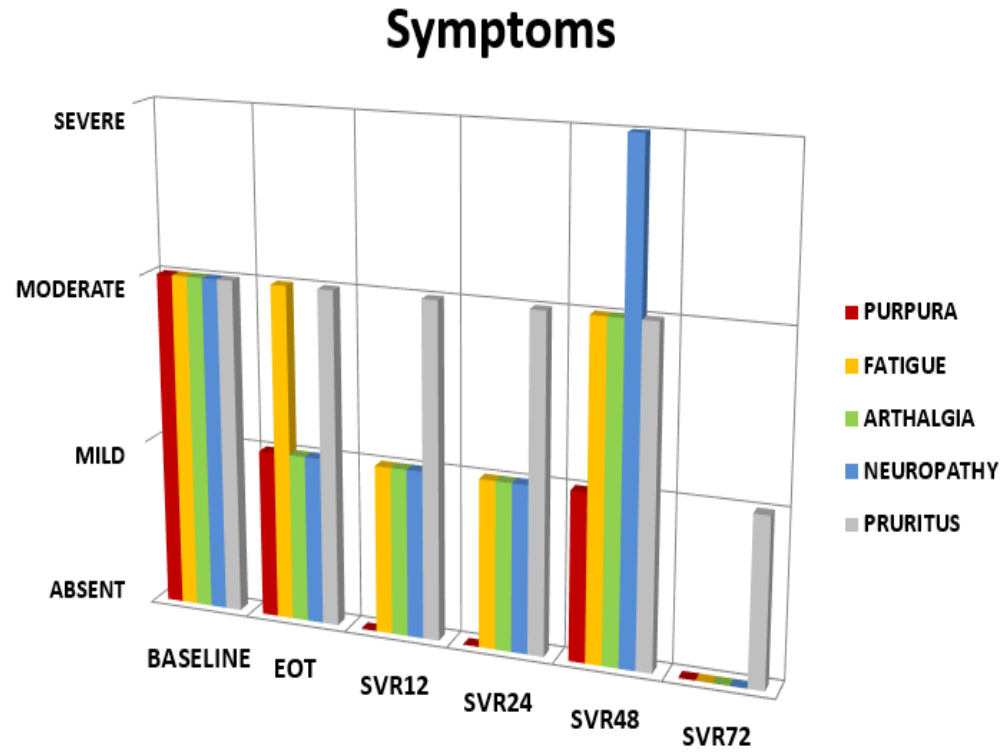


Relapsing patients: In 9 available cases Rel were characterized by high cryocrit levels before treatment and the persistence of cryoglobulinemia during the FU (even with improved cryocrit levels); in all but one case (temporary relapse) stigmata of LPD evolution were scored (e.g., suspected BMBx, non cirrhotic splenomegaly, lymphoadenopathy, diffuse itching and nocturne sweats, fever, MG, and high B2M levels)

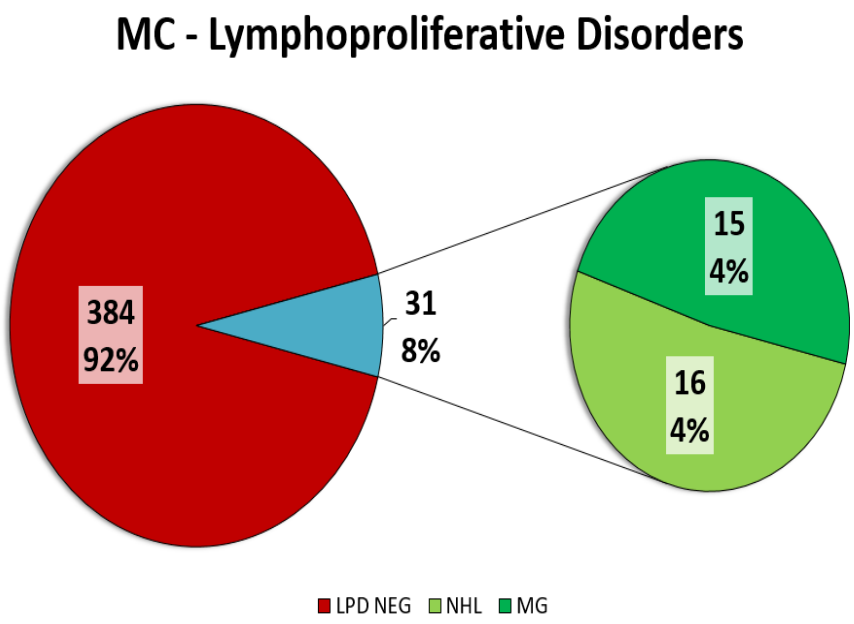
Post Treatment Symptoms in SVR patients=

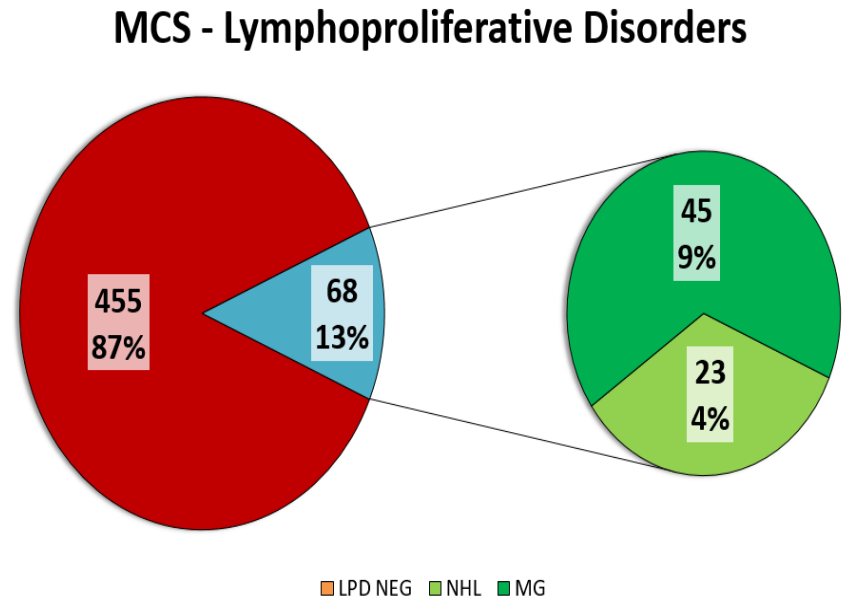
A Temporary Relapse case





Patients with MC showing different LPDs (Lymphoma or Monoclonal Gammopathy)





Antiviral Therapy in patients with MCS: PRELIMINARY RESULTS

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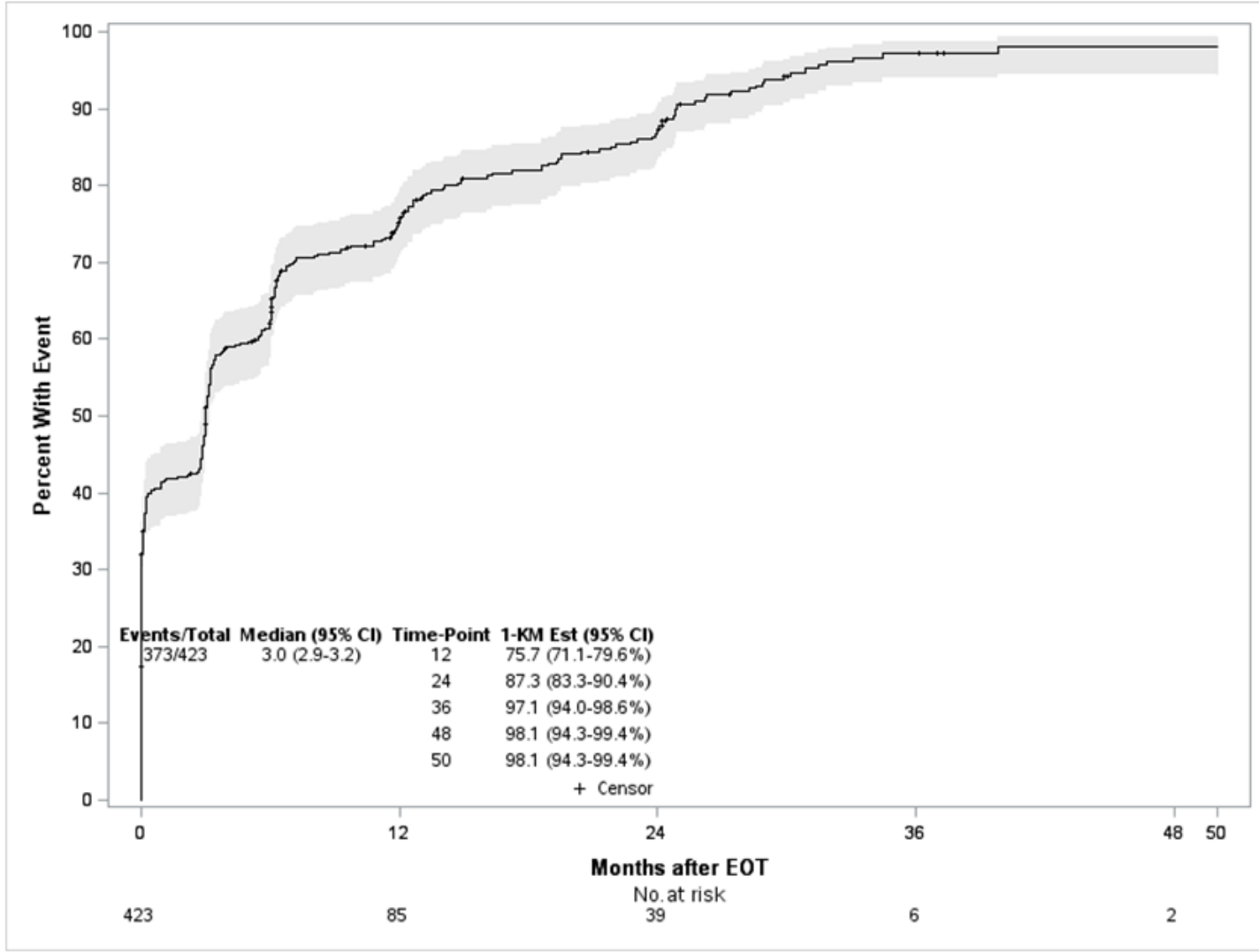
FIRST TIME OF CLINICAL RESPONSE



Antiviral Therapy in patients with MCS: PRELIMINARY RESULTS

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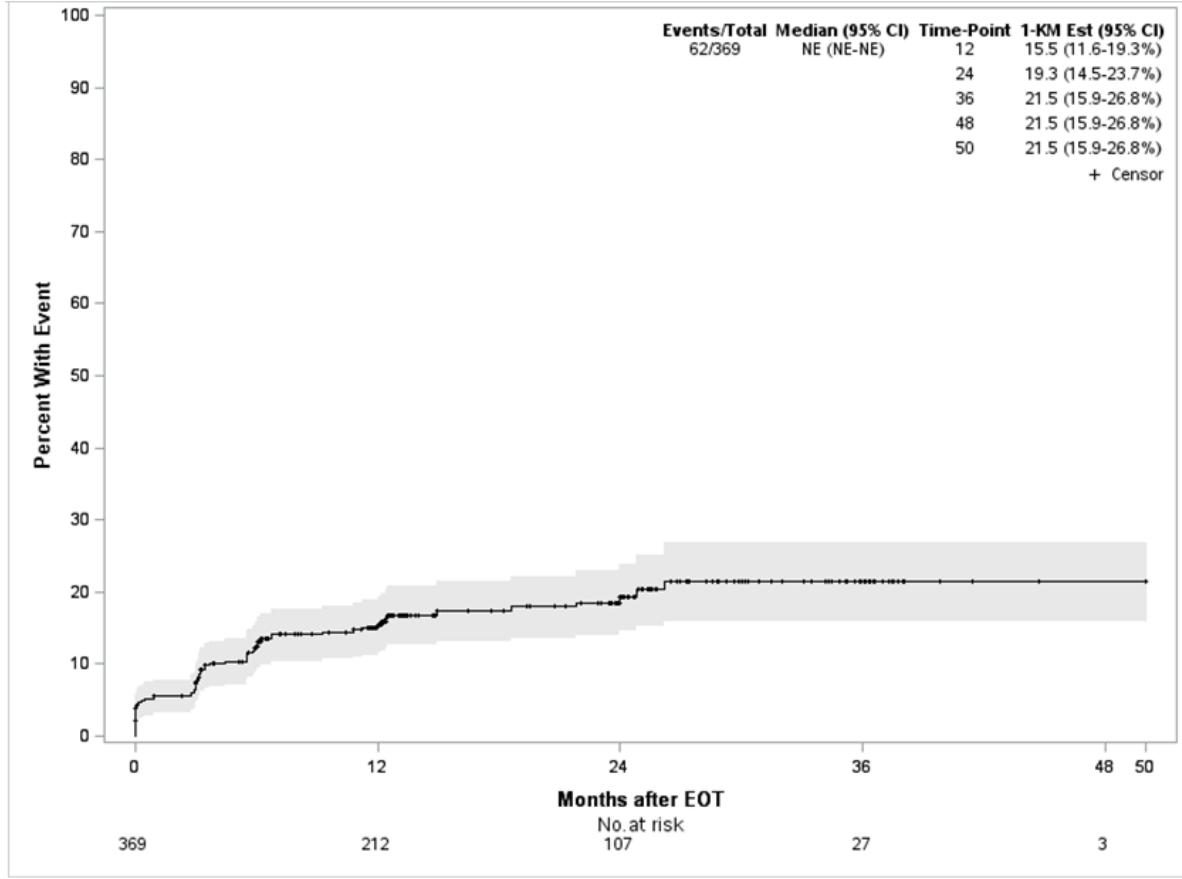
FIRST TIME OF FULL COMPLETE CLINICAL RESPONSE

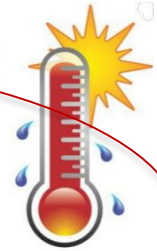


Persistence of laboratory and/or clinical MC stigmata after viral eradication

«Cold» Causes: low to very low evolutive risk

- ✓ **short f-u and/or Kupffer cell impairment in clearing CICs, especially in cirrhosis**
- ✓ **Presence of irreversible damages (eg. neurological axonal)**
- ✓ **Role played by a rebound effect after removal of previous therapies, especially in cases of symptoms exacerbations**

«Hot» Causes: high evolutive risk



- ✓ **Overcoming pathogenetic no-return points**
- ✓ **Evolution to NHL**
- ✓ **Possibility of occult HCV infection after DAAs (suggested, but no data on MC)**

Zignego et al, Hepatology, 2017

HCV+ LPDs Pathogenesis

Direct/indirect/others?

cytokines (BAFF)	E2 - CD81 binding	HCV proteins	B-cell infection

HCV-induced mutagenesis

Some SNPs from different genes/gene systems are presently associated with a higher risk of lymphoproliferative disorders during HCV chronic infection, amongst them:

- The baff (B-cell Activator Factor) system: gene rs12428930/promoter rs9514828 /receptor rs61756766;

  Giannini C. et al, Blood 2008; Gragnani L. et al, Arthr & Rheum 2011; Lake-Bakaar G et al, Clin Exp Immunol. 2012; Ayad MW et al, Mol Diagn Ther. 2015

- The HLA class II rs9461776 and the NOTCH4 rs notch4 rs2071286.

  Zignego AL et al, Genes & Immunity 2014, Gragnani L et al, Oncotarget 2017; Artemova M, Dig Liver Dis. 2018

Mixed Cryoglobulinemia

Additional genetic aberrations

Malignant NHL

HCV

Evaluation of B-cell clonality and genetic markers in HCV-SVR MCS patients with (Group B) and without (Group A) persisting symptoms

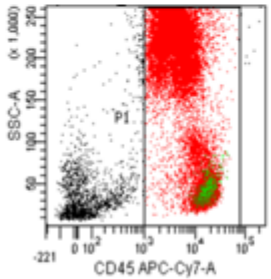
98 HCV SCM SVR patients (53 with persisting complete clinical response and 45 patients with SCM persistence/recurrence after AVT were prospectively evaluated during the long-term follow-up (mean 15 m)

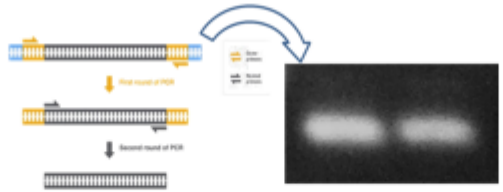
Stored samples from 75 patients (38 and 37, respectively) at therapy baseline were also evaluated

1) Flow-cytometry

B-cell surface κ/λ ratio

(on whole blood samples)

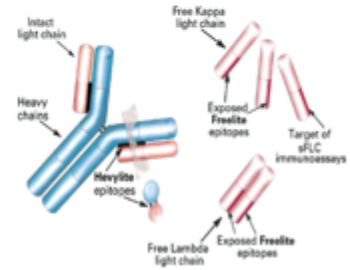




2) Nested-PCR for t(14;18)

(on DNA extracted from peripheral blood mononuclear cells)

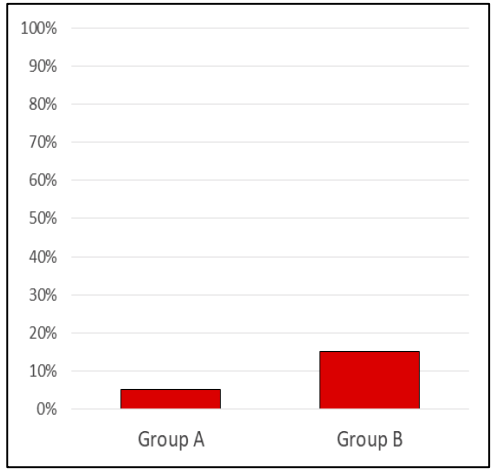
3) Immunoassay for Free Light Chains ratio (κ/λ) assay (on plasma samples)



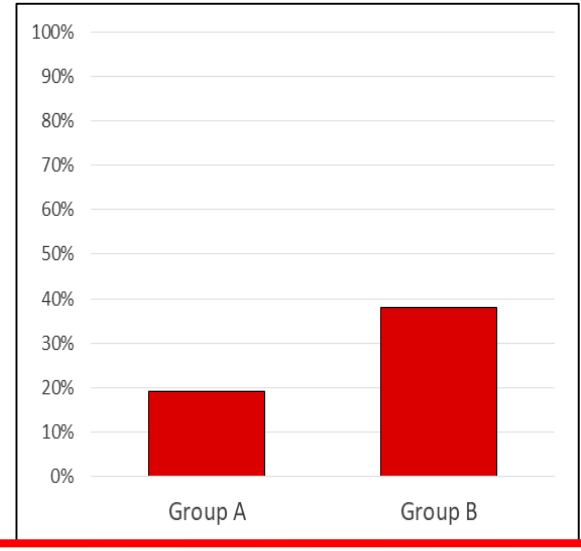
RESULTS I (a: after therapy; b: before therapy)

a

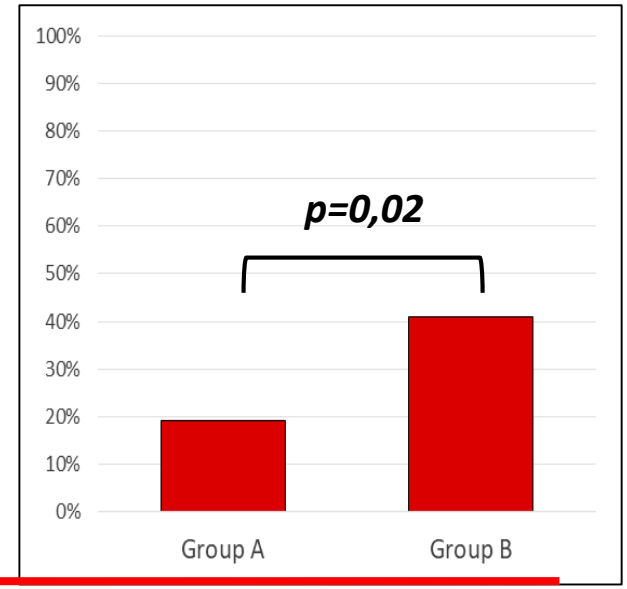
Flow cytometry (B-cell surface κ/λ ratio)



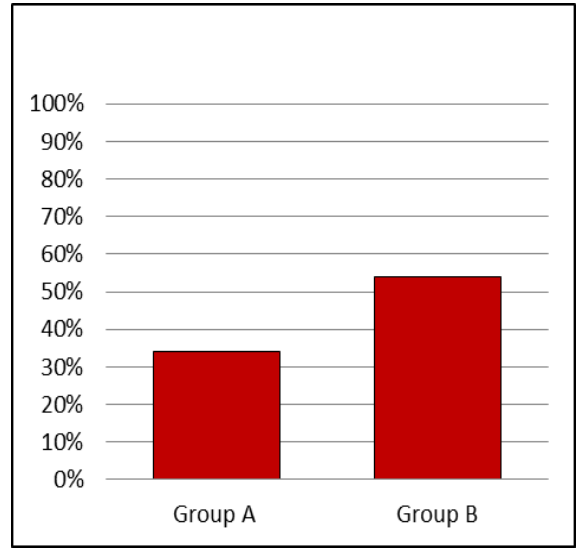
T(14;18)

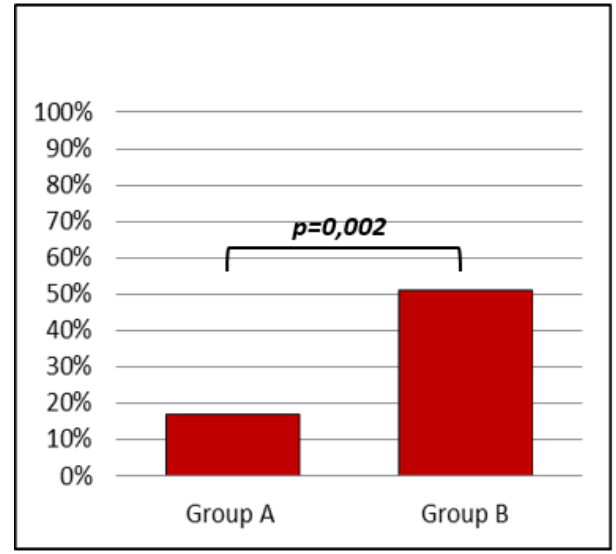


FLC κ/λ ratio

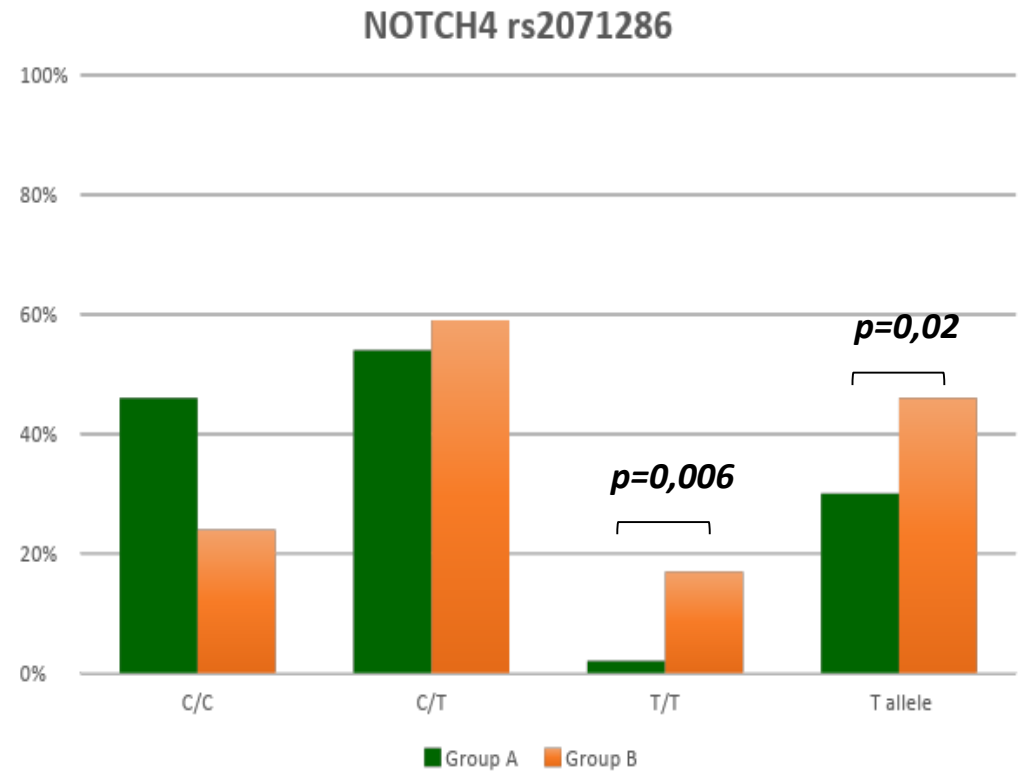


b





RESULTS II
NOTCH 4 rs2071286 ANALYSIS



CONCLUSIONS

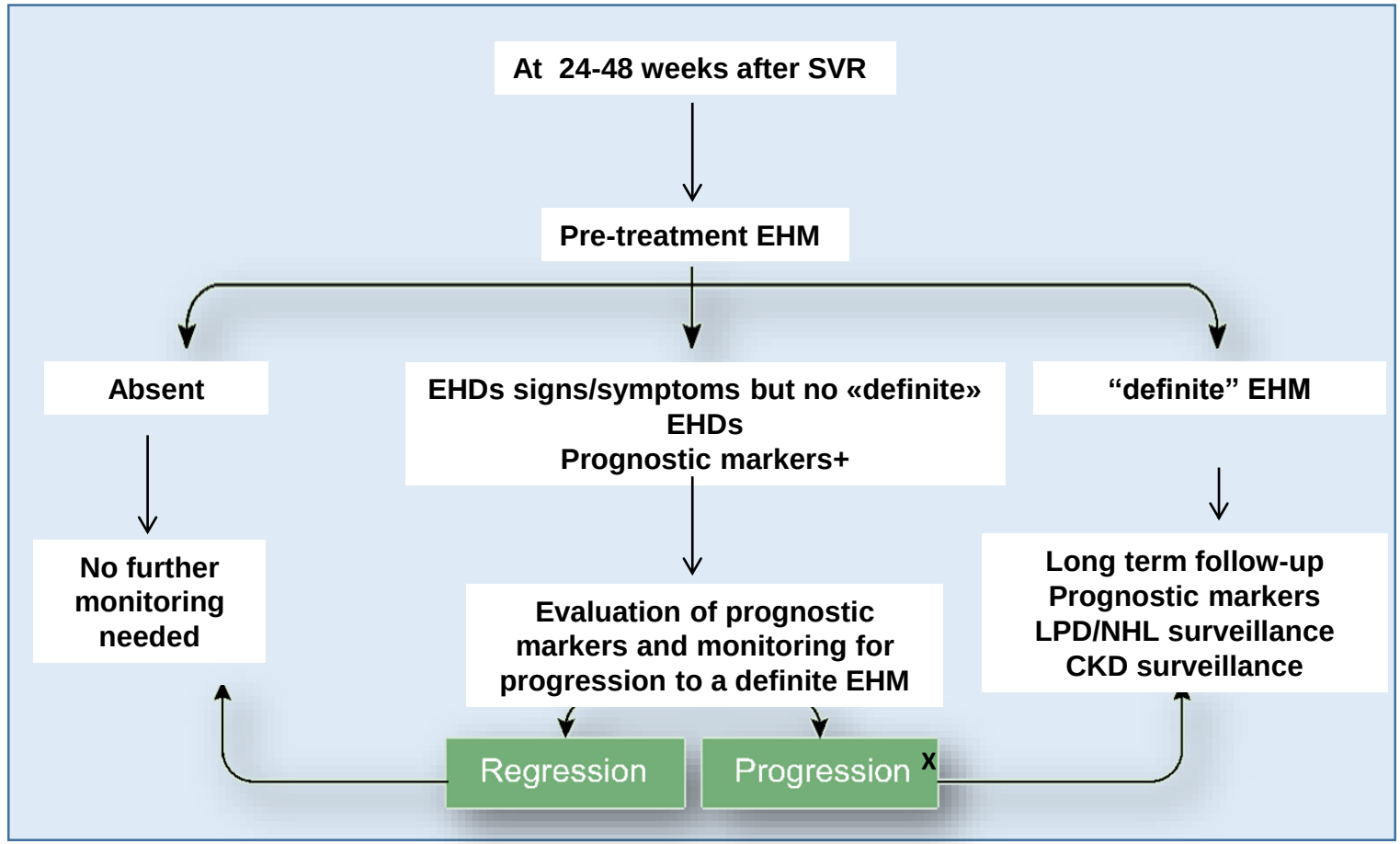
- Amongst the clonality biomarker, FLC κ/λ ratio proved to be the most strongly associated with the persistence of MC after HCV eradication, both before and after therapy

- The significant association between notch4 rs2071286 minor allele and persistence/relapse of CV after a SVR suggests that this SNP could also represent an early biomarker for CV persistence/recurrence in the post-therapy follow-up. Further studies will be useful in order to better set-up and characterize such a new marker

- Clinical response outcome predictors could be precious for the assessment of a rational flow-chart to manage CV patients during the follow-up, thereby selecting the best therapeutic strategy and preventing further evolution towards malignancy

Taylored Post AVT Follow-Up of HCV-MC Patients

B-cell clonality & genetic tests



*Consider RTX treatment in persisting B-cell clonality

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Post Treatment Symptoms in patients achieving SVR12 (EOFU)

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

Disappearance of all Symptoms

in 93 (27%)

Improvement of all Symptoms

in 101 (29%) pts

Improvement of more than 50% of symptom

in 78 (23%) pts

NO Improvement in more than 50% of symptor

in 61 (18%) pts

Relapse

in 13 (4%)

No available data

in 48

Cutaneous Manifestations (Purpura) were the most rapidly responsive ones

Full complete

Complete

Partial

CLIN RESP 272 (79%)

No response

NO RESP 74 (21%)