Studio degli outcome importanti della malattia del fegato:
L'epatocarcinoma nei pazienti che hanno eliminato HCV

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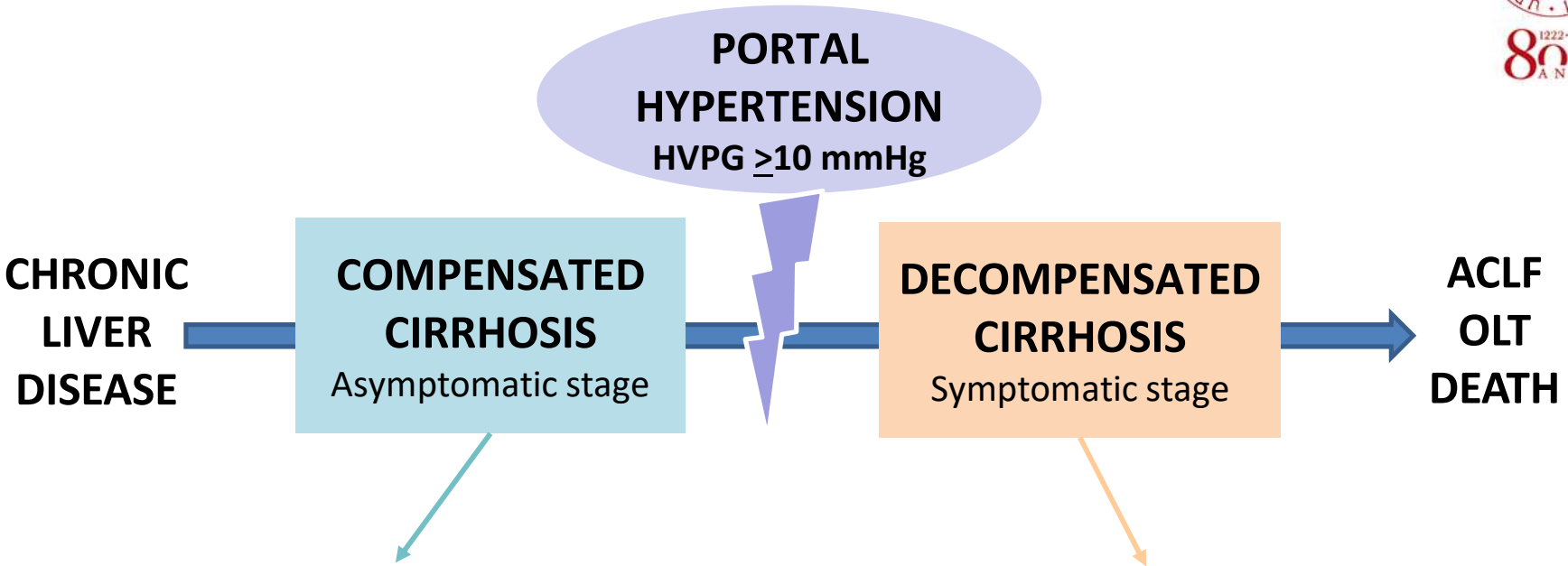
The goal of DAA treatment in chronic hepatitis C

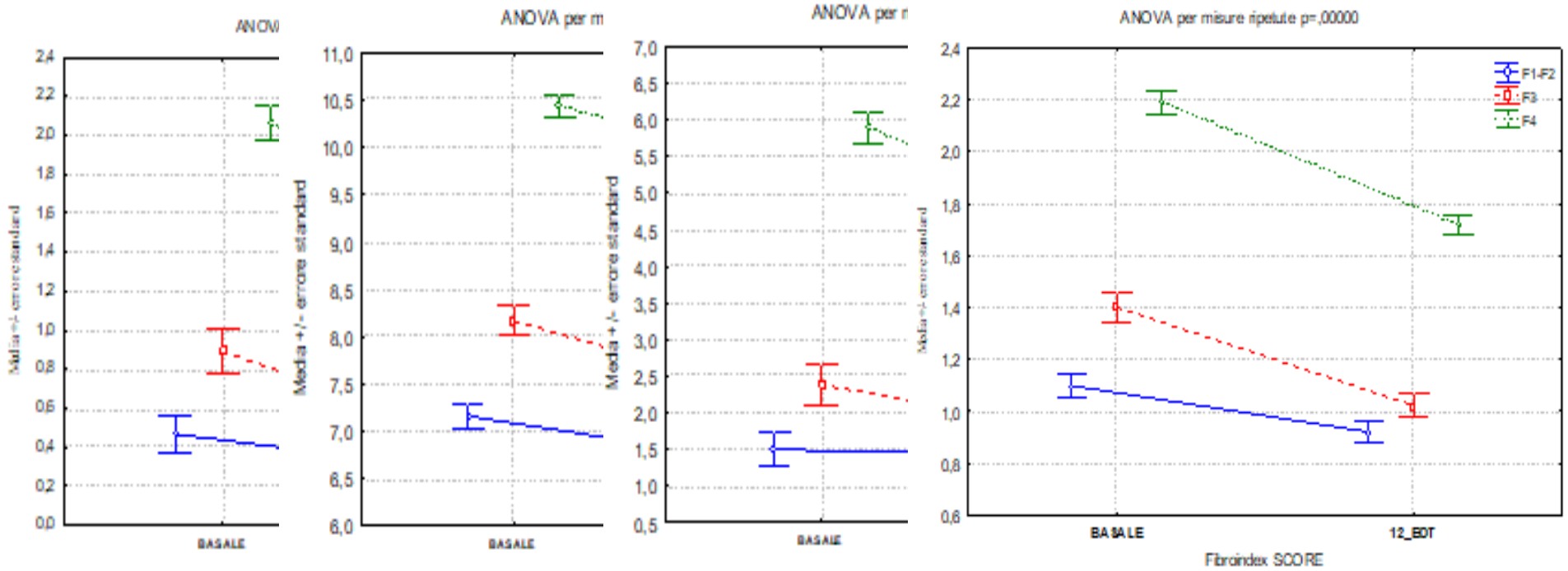


- ✓ Promote fibrosis regression
- ✓ Reduce portal hypertension
- ✓ Improve liver dysfunction
- ✓ Abolish HCC risk

- ✓ Prevent further decompensation
- ✓ Prevent HCC
- ✓ Impede ACLD
- ✓ Decrease OLT/Death

Regression of staging scores for fibrosis after DAA

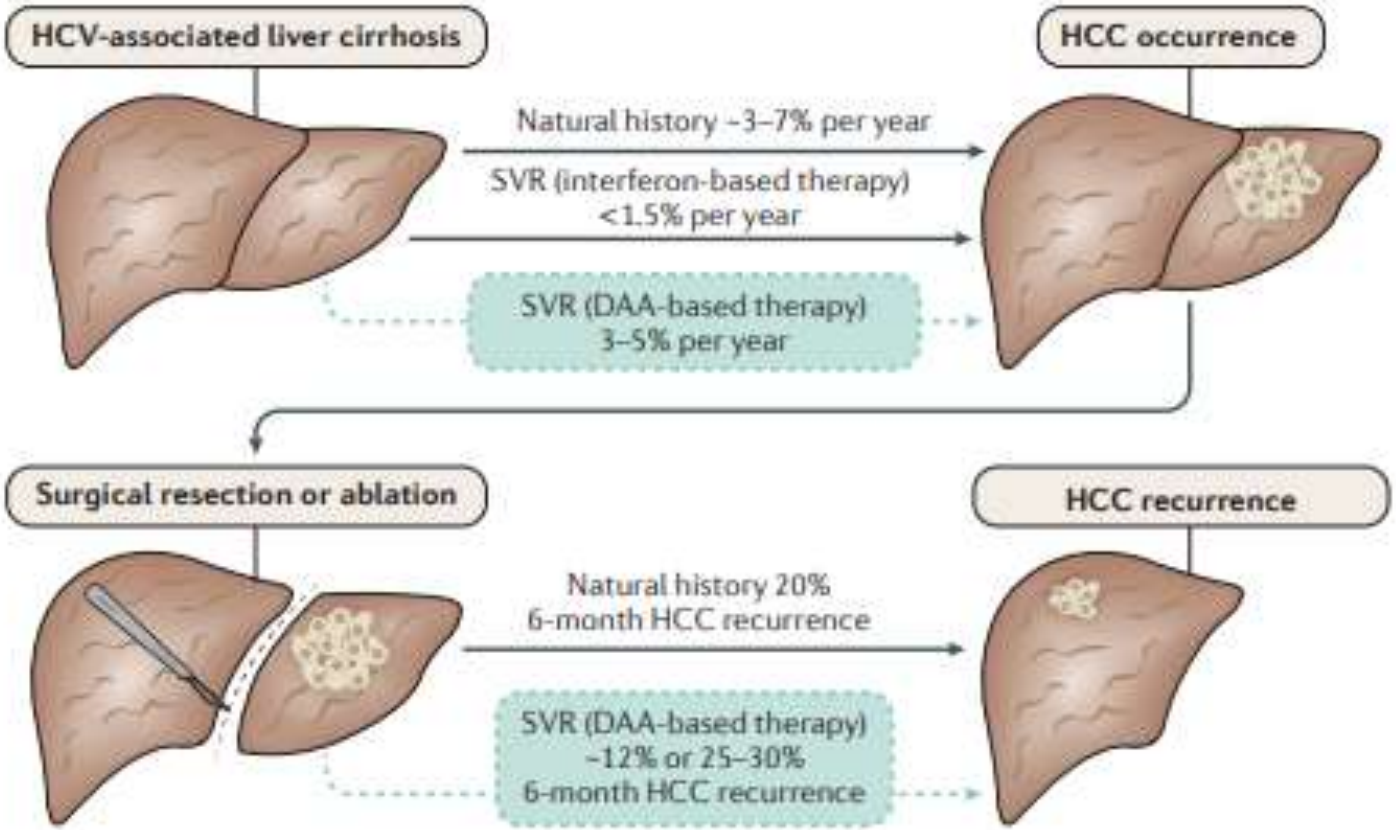
Stadiazione non invasiva della FIBROSI	BASALE			12 mesi dopo terapia (12_EOT)		
STADIO sec. METAVIR	**F2**	**F3**	**F4**	**F2**	**F3**	**F4**
SCORE DI:						
APRI (media) > 1,5	0,5	0,9	2,1	0,3	0,3	0,8
FORNS (media) > 6,9	7,1	8,2	10,5	6,7	7,2	9,6
FIB-4 (media) > 3,25	1,5	2,4	6,1	1,4	1,7	4,0
Fibro-INDEX (media) > 2,25	1,1	1,4	2,2	0,9	1,0	1,7



467 patients with chronic hepatitis C: F2-F3 in 273, cirrhosis CPT-A in 157 and CPT-B in 40 cases.

Natural history and SVR after IFN or DAA impact on HCC occurrence and recurrence rates per year

The impact of DAA therapy on HCC incidence has been subject to significant debate

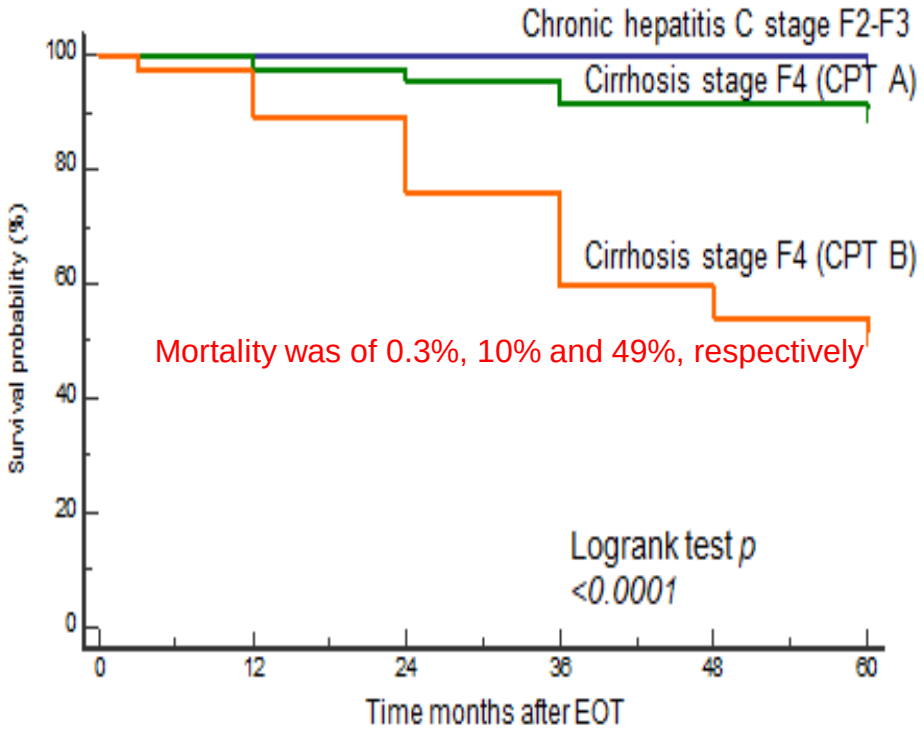


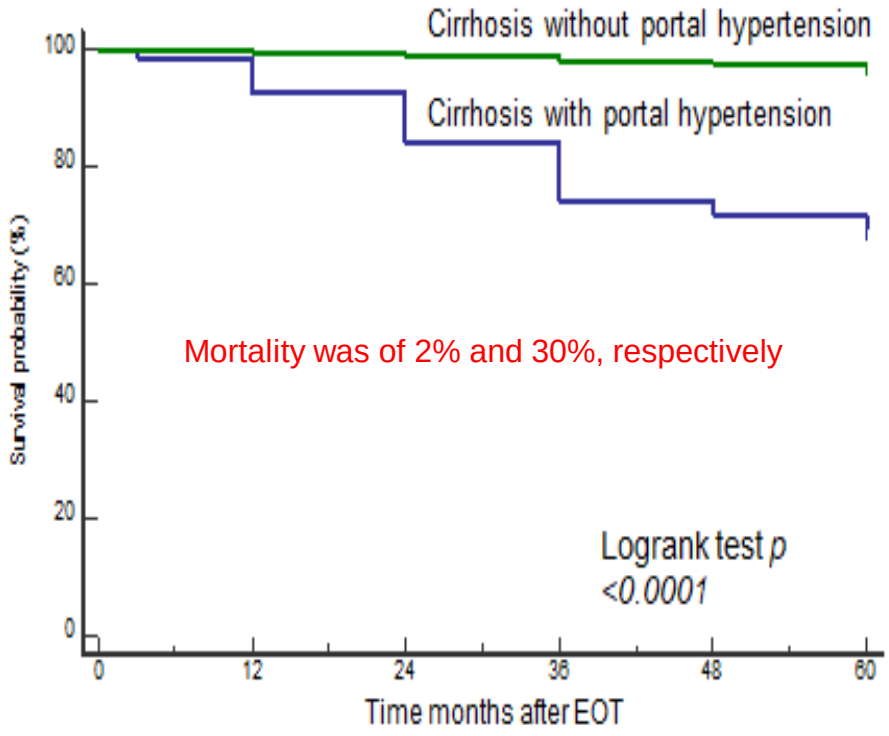
Conti F.et al. J. Hep.2016; Reig M.et al. J..Hep.2016; Llovet JM.et al. Nature Rev.2016; Sapena V.et al. Gut 2020

Mortality due to liver-related events after DAA in relation to Child and portal hypertension

48 months Kaplan-Meier estimation survival

467 patients with chronic hepatitis C: F2-F3 in 273, cirrhosis CPT-A in 157 and CPT-B in 40 cases.





Liver-related events occurred in 48% of cases

over 65 years of age

DE NOVO HEPATOCELLULAR CARCINOMA OCCURRENCE AFTER HCV VIRAL ERADICATION BY DAA:

MID TO LONG-TERM OBSERVATIONS FROM THE ONGOING PITER COHORT

LA Kondili, MG Quaranta, L Cavalletto, L Ferrigno, C Coppola, DC Amoruso, G Brancaccio, G. Raimondo, R Filomia, MR. Brunetto, B Coco, AL Zignego, M Monti, A Iannone, S Madonia, D Ieluzzi, G Taliani, E Biliotti, G Verucchi, L Badia, G Migliorino, I Beretta, M Massari, A Licata, A R Capitano, F Barbaro, M Zuin, A Giorgini, M Persico, M Masarone, F P Russo, A Zanetto, F Morisco, V Cossiga, P Blanc, P Pierotti, A Craxì, V Calvaruso and L Chemello on behalf of PITER Collaborating Group.

A Real-life Observational Multicenter Italian PITER cohort

- ✓ HCC is an adverse outcome developed in patients with HCV related liver disease.
- ✓ The risk of *de novo* HCC appraisal persists after HCV eradication by DAA therapy, particularly in patients with liver cirrhosis.
- ✓ We aimed to evaluate the mid to long-term DAA treatment impact on *de novo* HCC development in patients with cirrhosis.

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

Baseline characteristics of 2214 patients with cirrhosis by *de novo* HCC after DAA

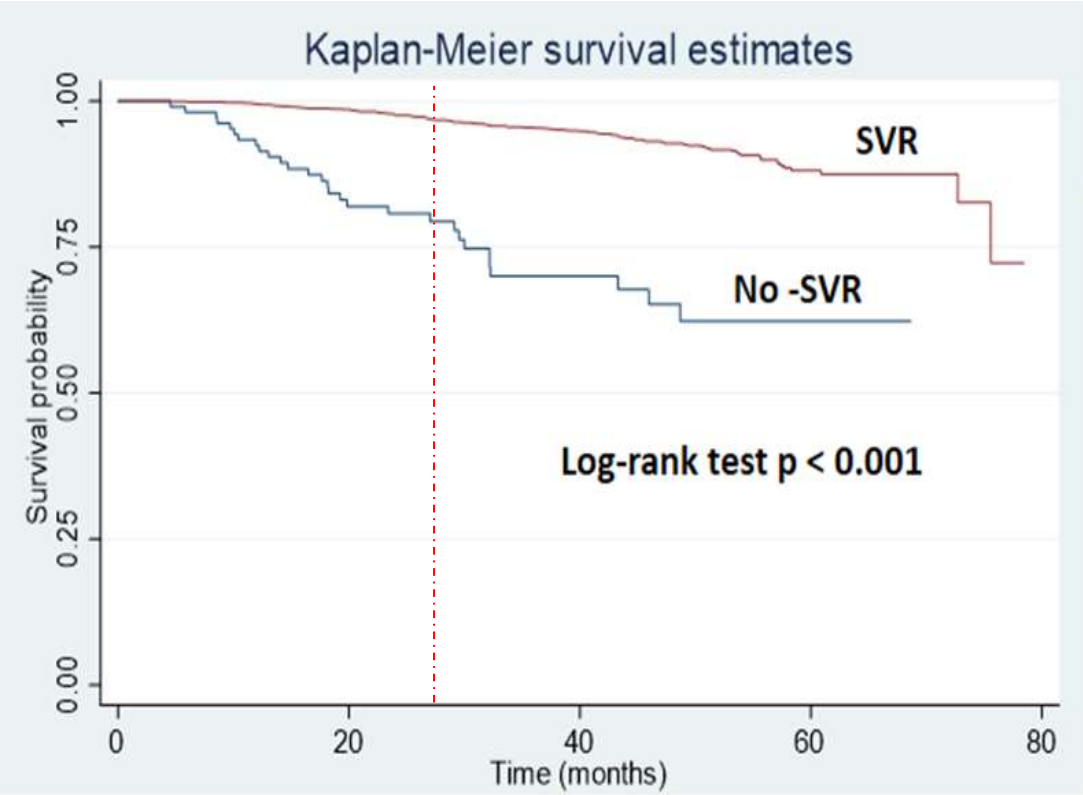
		No HCC (N=2065*)		De novo HCC (N=149*)		
Baseline data		Median (IQR)		Median (IQR)		p**
Age (years)		64 (54 - 71)		67 (60 - 71)		**0.002**
Liver Stiffness Measurement (kPa)		18.8 (14.5 - 26.6)		21.8 (17.0 - 31.5)		**0.008**
		N.	%	N.	%	p***
Platelets count	≤ 150,000/µL	1409	70.6	127	87.6	**< 0.001**
	> 150,000/µL	588	29.4	18	12.4	
Albumin (g/dL)	≤ 3.5	438	23.7	63	44.4	**< 0.001**
	> 3.5	1408	76.3	79	55.6	
FIB4	≤ 3.25	653	33.0	25	17.4	**< 0.001**
	> 3.25	1328	67.0	119	82.6	
Child-Pugh Class	A	1755	85.0	117	78.5	**0.035**
	B	310	15.0	32	21.5	
Ascites		147	7.1	20	13.4	**0.005**
Esophageal varices		436	21.1	53	35.6	**< 0.001**
Previous decompensations		229	11.1	26	17.5	**0.015**

No differences were observed between cases without and with development of *de novo* HCC by gender, BMI, Alcohol use, HCV-genotype, HBV and HIV coinfections, IFN experienced, as well as by levels of ALT, AST, Bilirubin, Creatinine, INR (p=ns).

AASLD The Liver Meeting

HCC free survival analysis – time dependent by SVR

- ✓ SVR was achieved in 93% (2064 out of 2214) of cases and 119 (5.8%) developed *de novo* HCC.
- ✓ Among 150 patients without SVR, 30 cases (20%) developed HCC. HR=7.38 (95% CI 4.27-12.78) (p<0.01)
- ✓ A total of 149 (6.7%) patients developed *de novo* HCC with:
  - an incidence rate of 2.8 per 100 p-yrs
  - a median follow-up of 30 months from EOT (IQR 20-43 mos) and
  - a median age of 64 yrs (IQR 54-71 yrs).
- ✓ The 24 months HCC free survival was 98% and 81% in patients with and without SVR achievement.



Variables associated with death in patients with SVR and *de novo* HCC occurrence after DAA

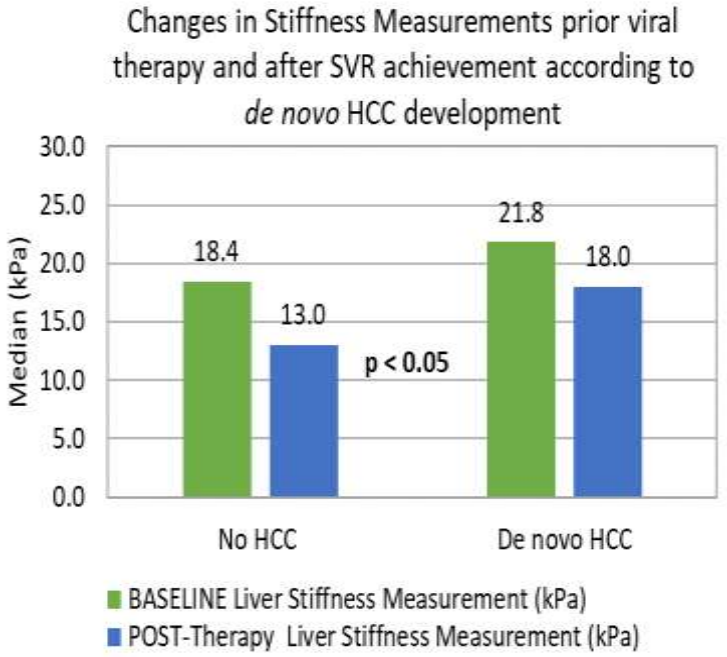
Of 119 patients who achieved the SVR and developed *de novo* HCC:

- ✓ 80% were diagnosed as HCC Stage A or B of BCLC classification.
- ✓ 26% of patients died and 8% underwent liver transplantation during FU.
- ✓ At the end of FU, 38% of cases had still an active HCC status.

Variables associated with death in HCC patients

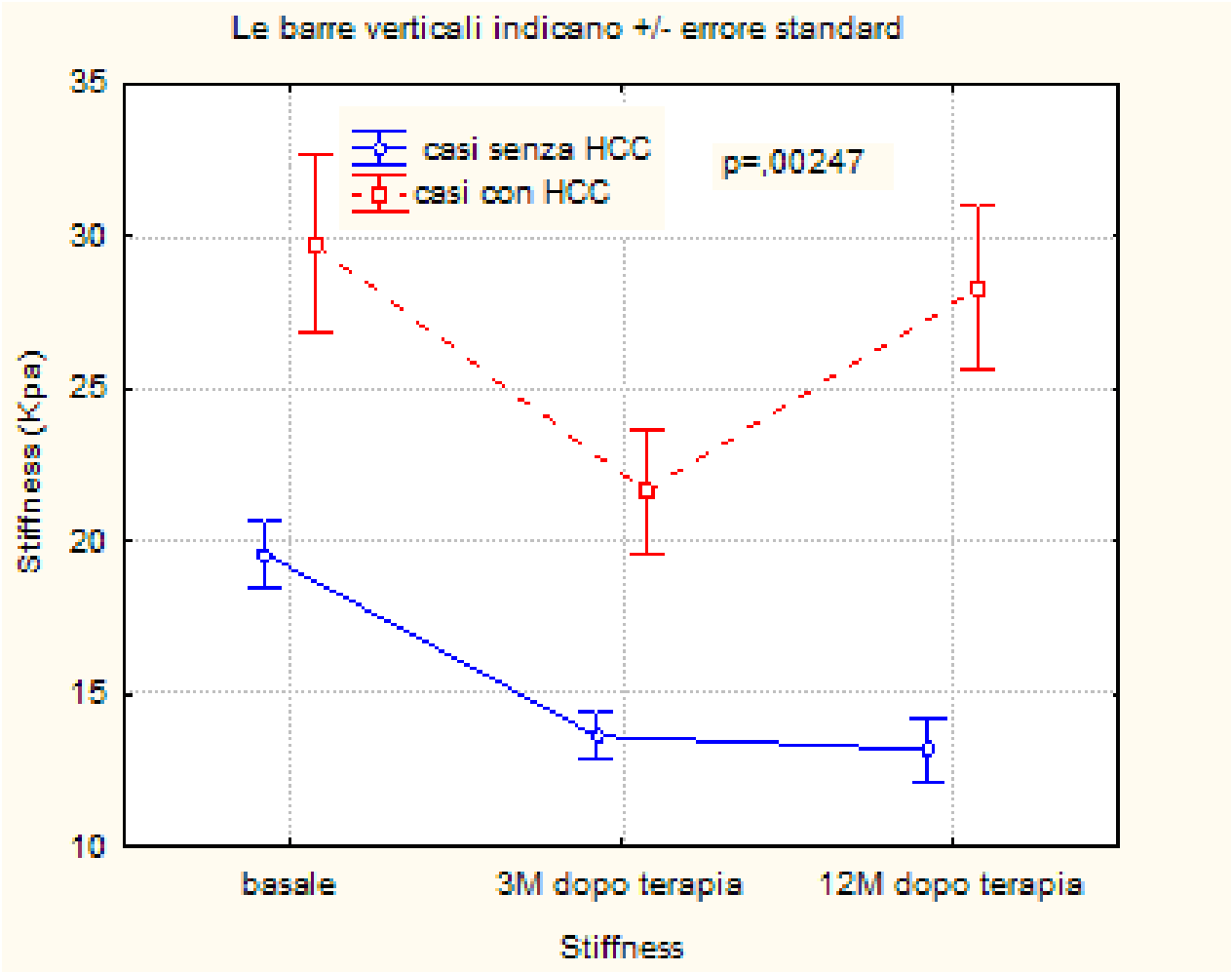
Baseline data	Crude HR	95% CI	Adjusted HR*	95% CI
AFP	1.01	0.98 - 1.03		
FIB-4	0.57	0.24 - 1.35		
Ultrasound basal spleen diameter (cm)	**1.13**	**1.02 - 1.26**		
Liver Stiffness Measurement (kPa)	**1.04**	**1.01 - 1.07**	**1.05**	**1.01 - 1.09**
Liver Stiffness-spleen size-to-platelet ratio	1.14	1.03 - 1.25		
Platelets (ref. >100,000/µL)	1.44	0.34 - 6.09		

High baseline liver stiffness (ranging from 17-31 kPa) resulted independently associated to death (HR 1.04; CI 95%: 1.01-1.09)



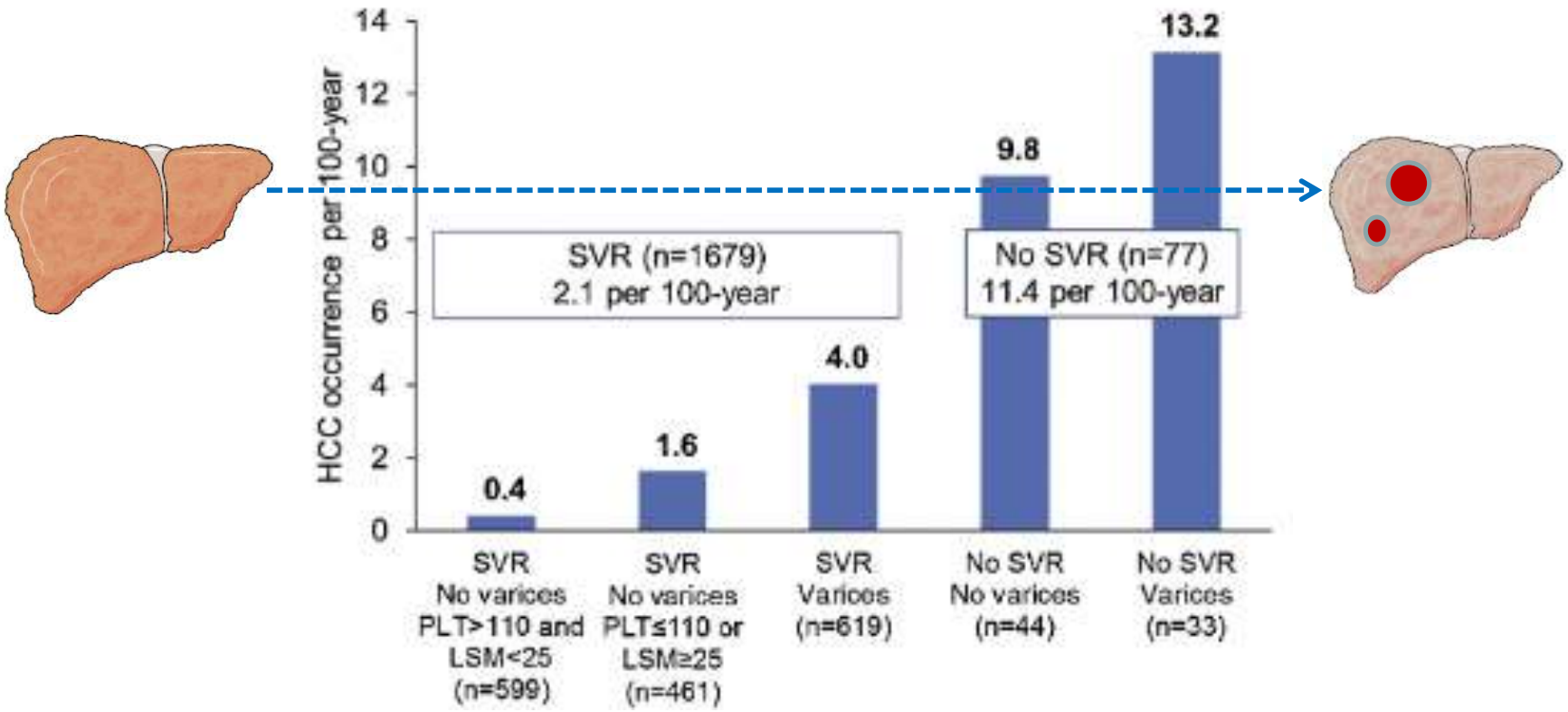
Early increase of LS values in cases with HCC development

Padua cohort 2015-2017: 197 cases with cirrhosis (CPT-A in 157 and CPT-B in 40 cases) of which 32 developed HCC (11% in CPT-A and 40% in CPT-B; *p<0.01*)



Rate of HCC occurrence (per 100-year) according to SVR status and history of esophageal varices

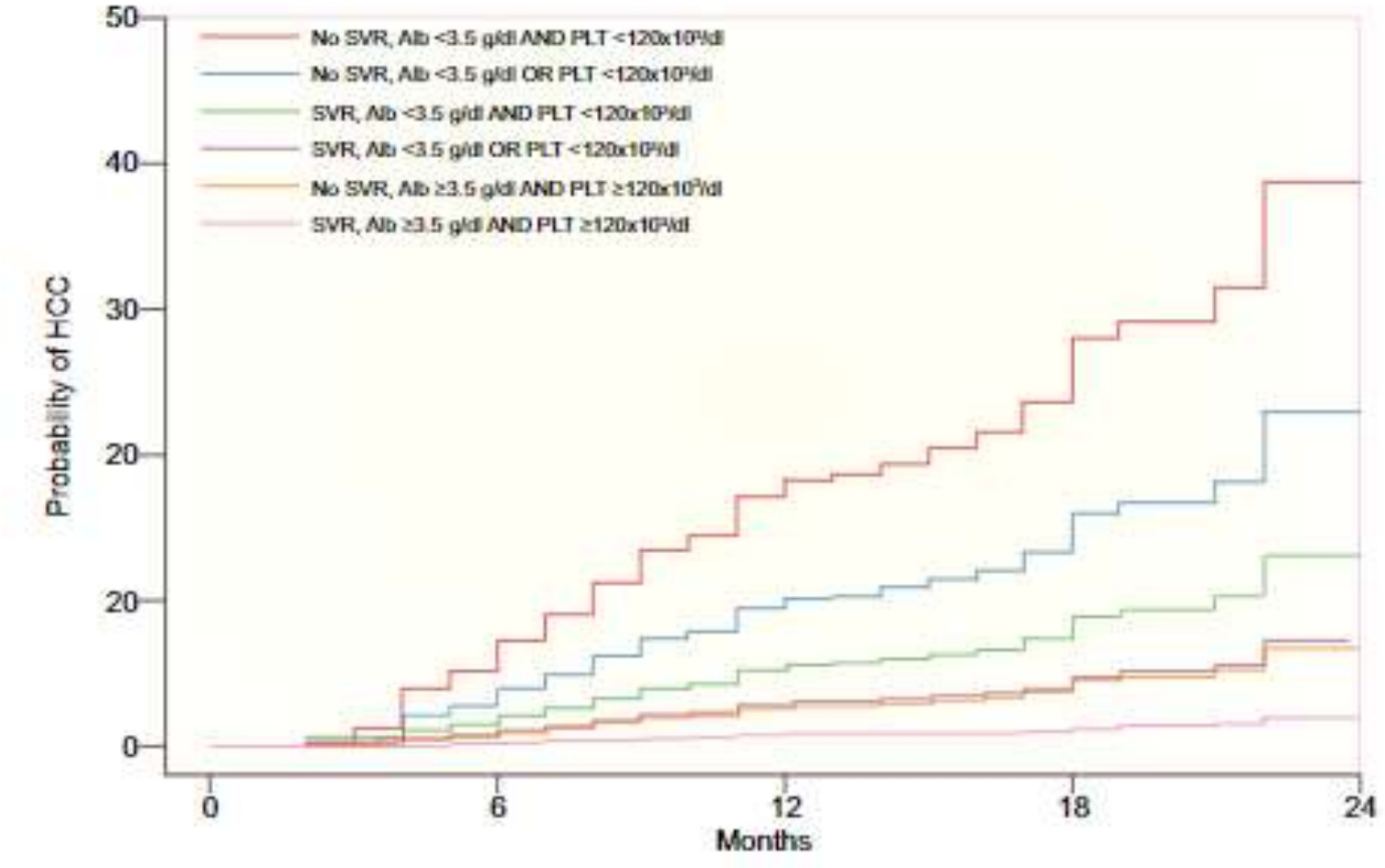
1927 consecutive HCV-infected cirrhotic patients treated with DAA from January to December 2015 in 10 tertiary liver centers in Italy and followed-up for 24 months. 34/161 patients had a previous HCC and recurred (24.8 per 100-year) and 50/1766 without a previous HCC history developed *de novo* HCC (incidence rate = 2.4 per 100-year).



Lleo A. et al. Dig and Liver Dis. 2019;51:310-317

Multi-parameter model for prediction of HCC after DAA

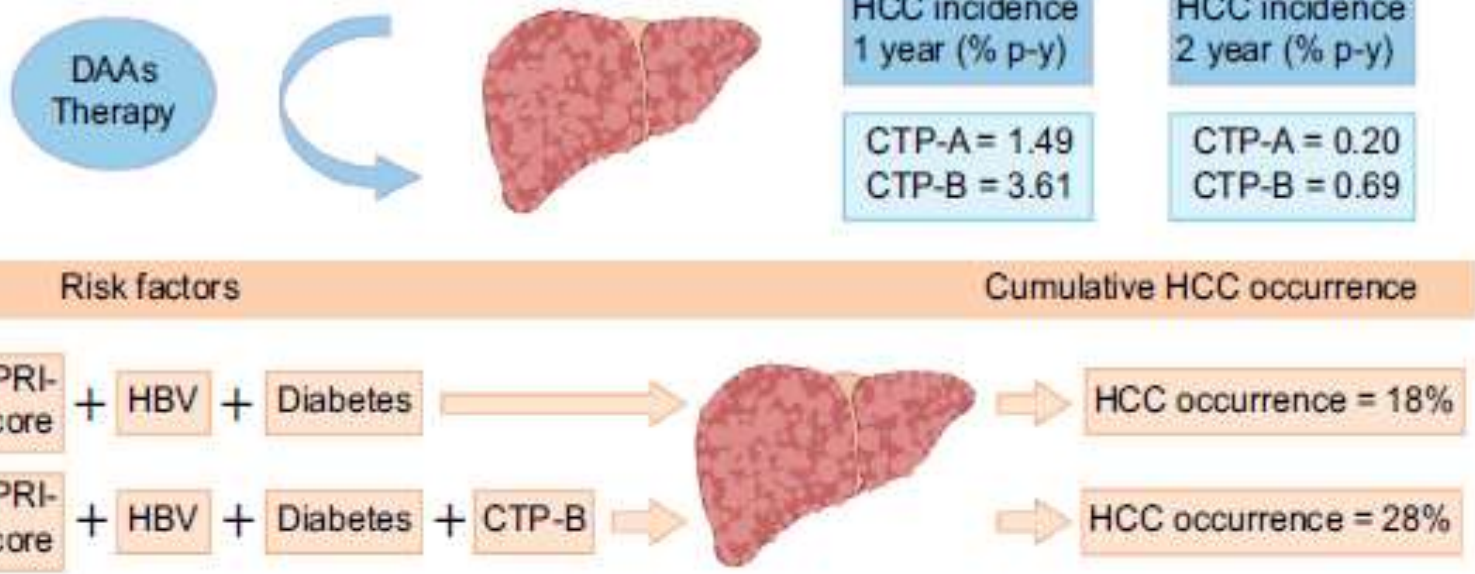
2,249 DAA-treated patients with cirrhosis prospectively included in the RESIST-HCV cohort



Calvaruso V. et al Gastroenterol. 2020:73;1578

The NAVIGATORE registry of the Veneto Region

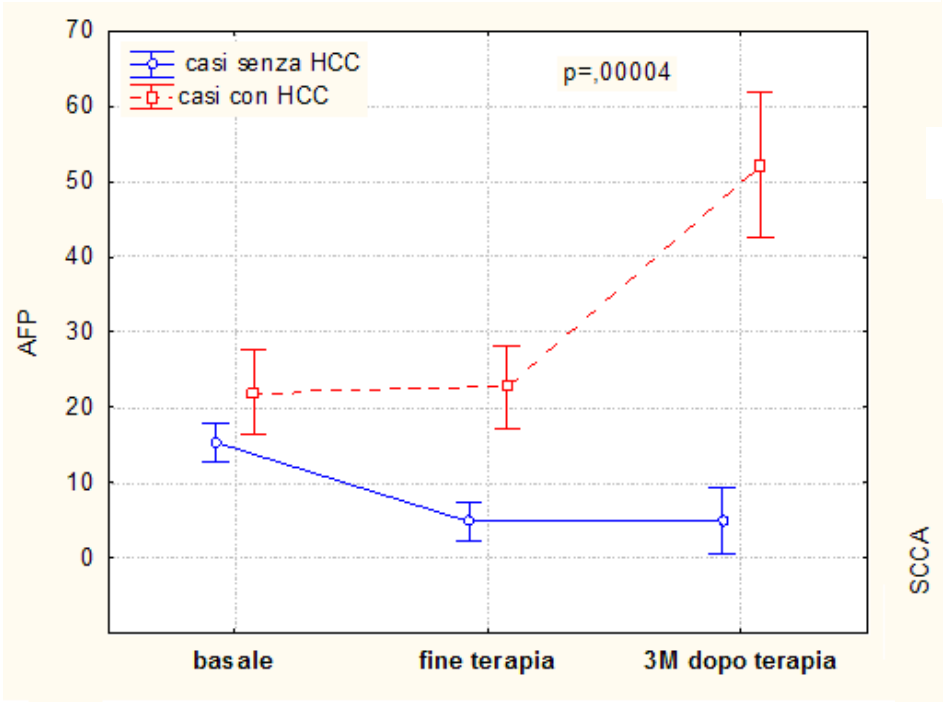
Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: a prospective population study



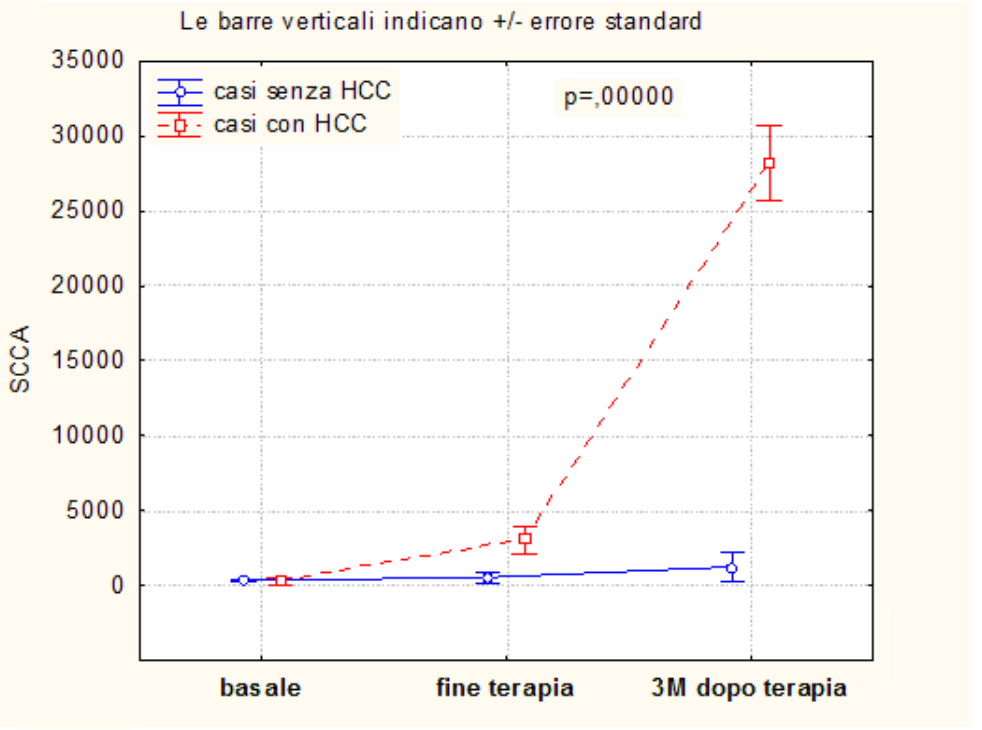
- ✓ Overall, HCC was diagnosed in 55/3917 patients. HCC incidence at first year was 0.46% (95% CI 0.12–1.17) in F3, 1.49% (1.03–2.08) in CTP-A and 3.61% (1.86–6.31) in CTP-B cases.
- ✓ Failure to achieve a sustained virological response was strongly associated with development of HCC (HR 9.09; 5.2–16.1; p = 0.0001).
- ✓ 29% of patients with HCC had an aggressive tumor, often seen early after DAA therapy.

Serum markers of *de novo* HCC development after DAA

*Alfa-1 fetoprotein (*AFP) levels

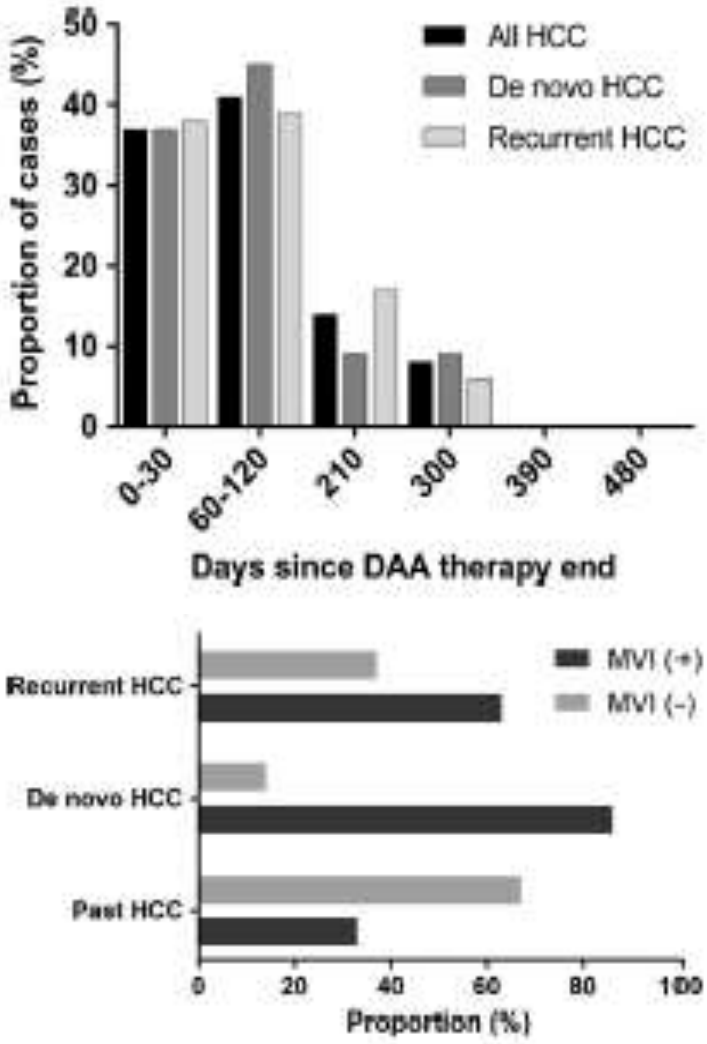


Squamous cells antigen (SCCA) levels



Padua cohort 2015-2017: 197 casi con cirrhosis, CPT-A in 157 and CPT-B in 40 cases.

MR imaging characteristic of HCC nodules after DAA



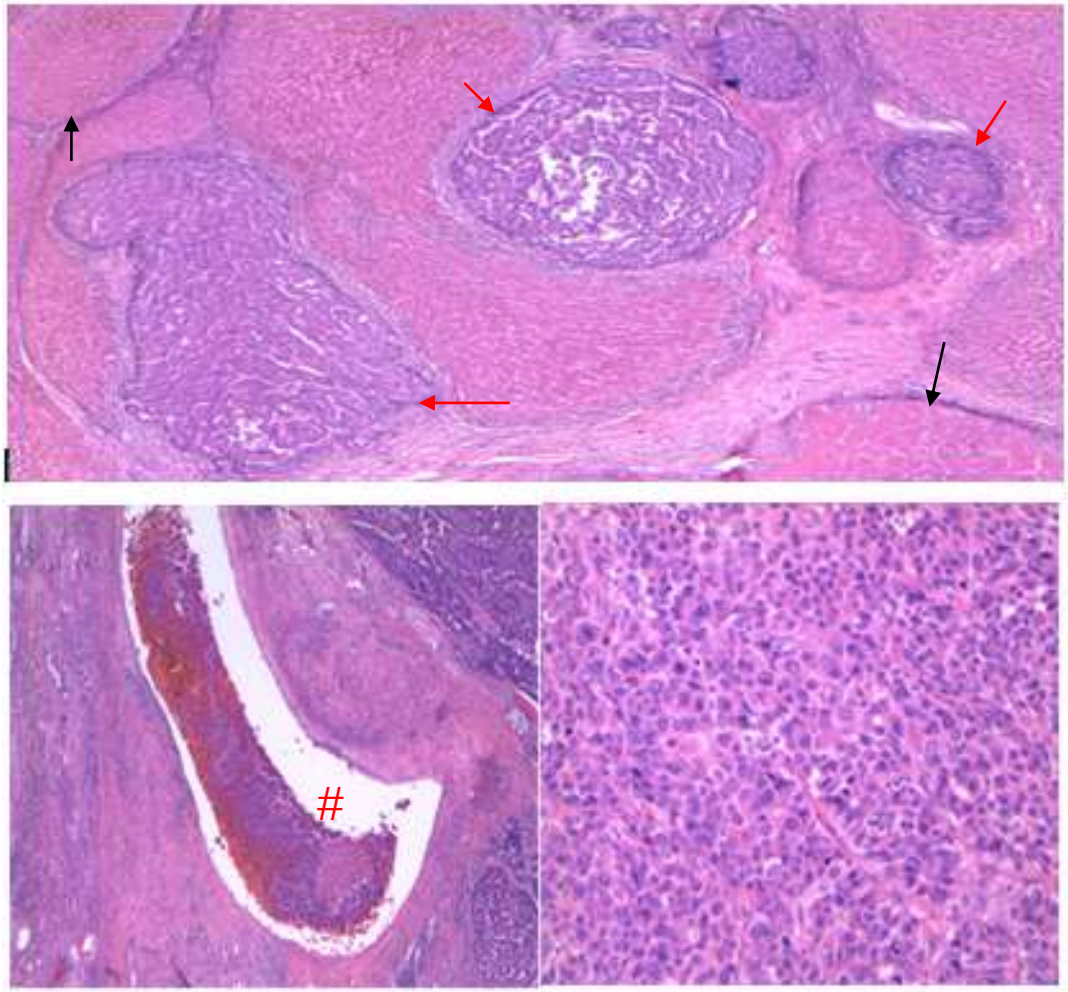
Retrospective cohort study on 344 consecutive patients with HCV-related cirrhosis treated with DAA.
After DAA, HCC developed in 29 patients (8.43%)(18 single and 11 multinodular). Incident de novo HCC occurred in 11 of the 285 patients without previous HCC (3.86%; 95% CI: 2.17–6.78) and in 18 of 59 patients with previous HCC (30.5%; 95% CI: 20.2–43.1).
Median interval between EOT and HCC diagnosis was 82 days (0–318). Maximum diameter was 10–20 mm in 27, 20–50 mm in 13, and > 50 mm in 1.
Imaging features of microvascular invasion were present in 29/41 nodules (70.7%, CI: 54–84), even in 17/29 nodules with 10–20 mm diameter (58.6%, CI: 39–76) and in only 17/51 HCC nodules that occurred before DAA treatment (33.3%, CI: 22–47) (p= 0.0007), furthermore it did not correlate with history of previous HCC.

Key Points

- In HCV cirrhosis, hepatocellular carcinoma develops soon after direct-acting antiviral therapy.
- HCC presents imaging features of microvascular invasion, predictive of more aggressive progression.
- Cirrhotic patients need aggressive and close monitoring after direct-acting antiviral therapy.

Renzulli M. et al. Eur Radiol (2018) 28:506–513

Hystologic characteristic of *de novo* HCC nodules



Cavalletto. et al. Cancers 2021 *submitted*

At microscopic observation the tumoral lesion appeared with multinodular and disseminated foci in several hepatic segments. The sample pattern resemble the *cirrhosis-like conformation* of the foci of HCC → arising between the nodules → of cirrhosis. A massive tumor growth with invasiveness of hepatic microcirculation # and high mitotic activity of neoplastic cells (histotype G2/G3) is observable.

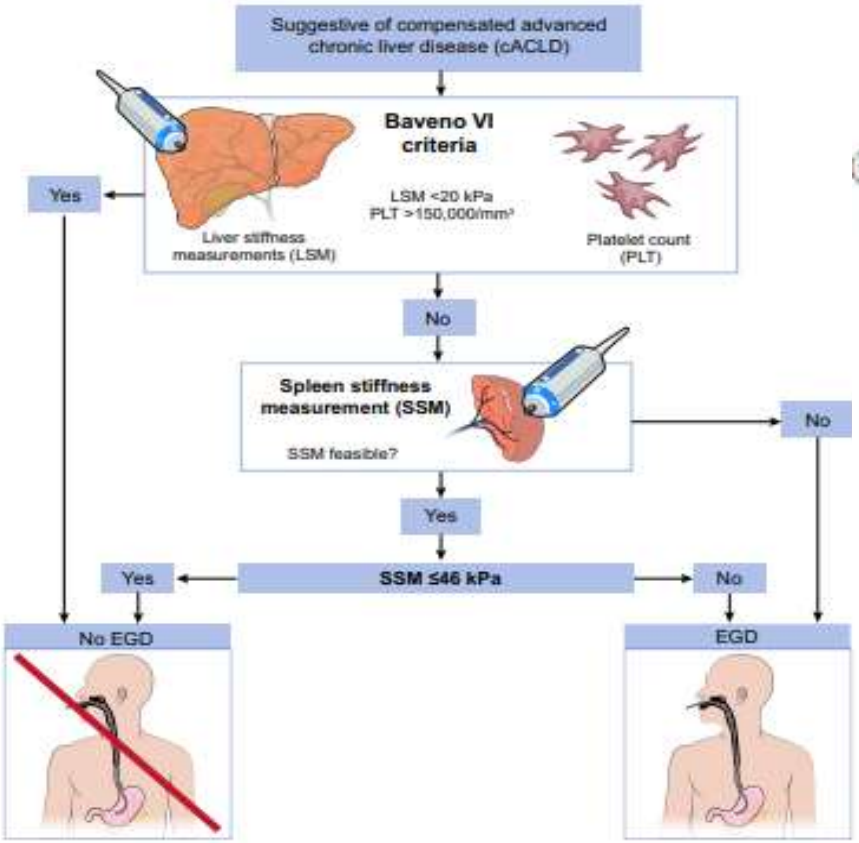
Predictors related to unfavourable outcome: *de novo* HCC[1], de-compensation[2], OLT[3] and death[4]

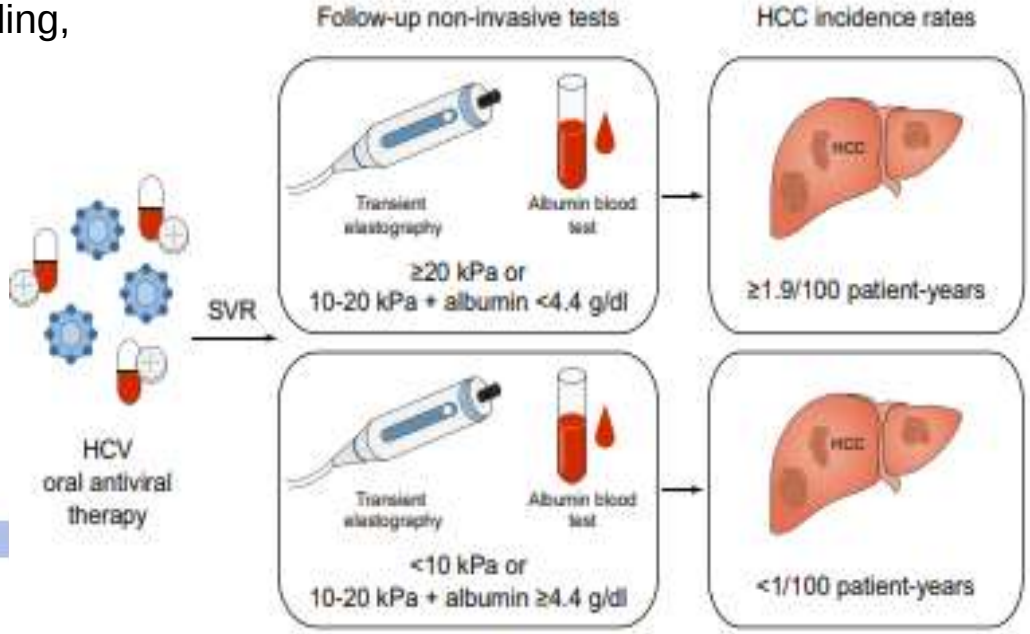
Predictors	ODDs Ratio	CI 95%	*p-value*
Liver stiffness values [1-2]	2.4	1.1-4.9	*0.02*
No SVR (Relapse/NR) [1-2-3-4]	7.7	3.2-20.6	*0.001*
EG varices presence [1-2-3-4]	3.8	1.5-19.9	*0.006*
History of HCC [1]	4.2	1.8-30.1	*0.001*
SCCA IgM levels [1]	5.3	2.5-31.2	*0.001*
Bilirubin levels [2-3-4]	1.1	1.0-1.4	*0.008*
Platelet count [2-3-4]	1.0	0.8-1.3	*0.04*

Non-invasive prediction of severe portal hypertension or liver related events after DAA therapy in patients with HCV

✓SSM is the most useful NITs to evaluate portal hypertension, presence of GEV and probability of decompensation.

✓SSM is an independent risk factor for bleeding, alongside LSM, platelet count and CPT-B.





Non-invasive prediction of liver-related events in patients with HCV-associated compensated advanced chronic liver disease after oral antivirals

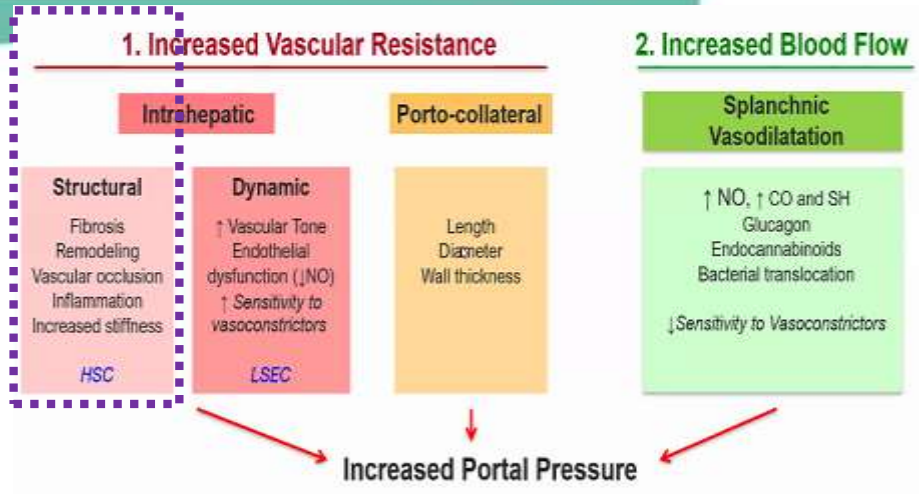
Colecchia A. et al. J Hepatol 2018;69:308-317

Pons M. et al. J Hepatol 2020;72:472-480

Stage-specifc features determining the probability of regression of portal hypertension and chronic liver disease is closely related to benefit of DAA-therapy

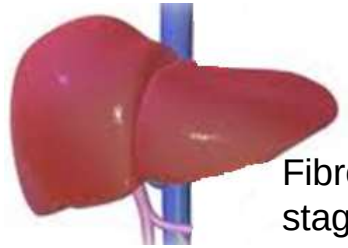
Clinical stage	Non-cirrhotic clinical manifestations	Compensated disease, no EV	Compensated disease, with EV	Decompensation: ascites, variceal hemorrhage, HE
HVPG	<5mmHg	5-10mmHg	≥10mmHg	≥12mmHg
Histological features	Steatohepatitis, F1-F3 fibrosis	Thin septa, big nodules	Broad septa	Very broad septa, small nodules
Cellular alterations	Necroinflammation, fibrogenesis, endothelial dysfunction	Fibrogenesis with cross-linking, angiogenesis	Parenchymal extinction	Insoluble, acellular scar

Impact of DAA



Absolute HCC incidence rate over time after DAA

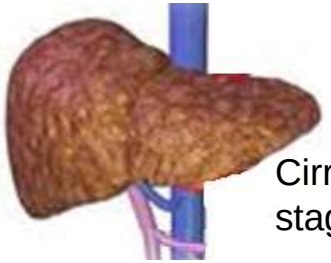
SVR reduced of about 70% the HCC risk



Fibrosis stage F3

95% benefit of DAA →

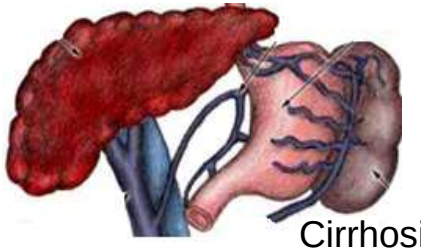
0.90 - 1.3% per year HCC occurrence



Cirrhosis stage F4

Child A — 75% benefit of DAA → 1.8 - 2.5% per year HCC occurrence

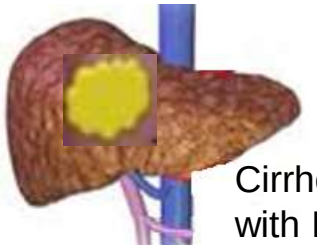
Child B — 25% benefit of DAA → 3.6 – 7.8% per year HCC occurrence



Cirrhosis with portal hypertension

10% benefit of DAA →

9.1 – 19.5% per year HCC occurrence



Cirrhosis with HCC

After curative treatment (resection/ablation)

?? benefit of DAA →

HCC recurrence
25-35% at 1 year
50-60% within 2 years

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Thanks

PITER

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