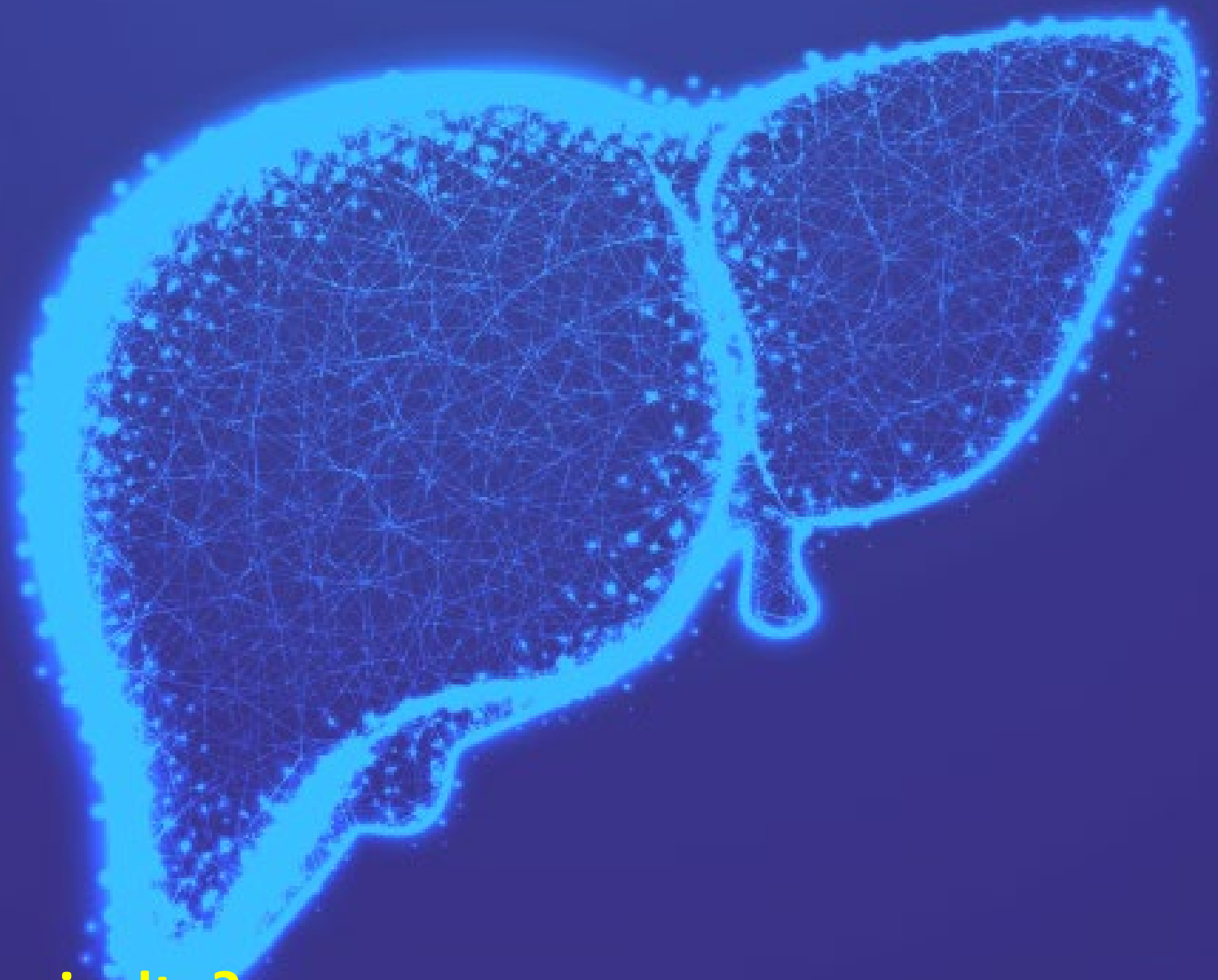
HCV IERI, OGGI... E DOMANI?

Reggio Emilia, 10 Marzo 2023
Sala Conferenze Laboratorio Aperto



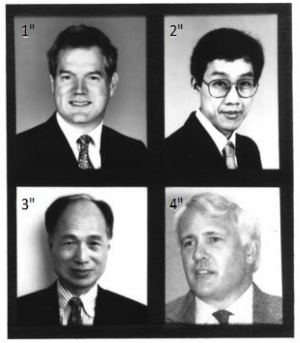
Foschi Francesco Giusppe

Direttore U.O Medicina Interna

Faenza AUSL Romagna

L’approccio Terapeutico:problema risolto?

From Virus Discovery to Plans for Elimination in 30 years



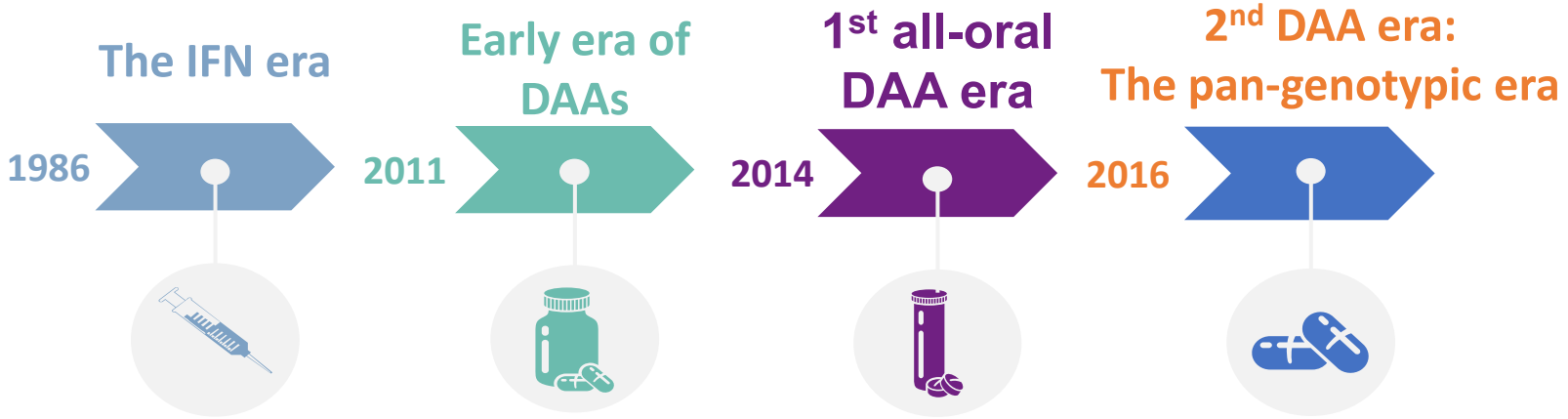
Science 21.4.1989

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

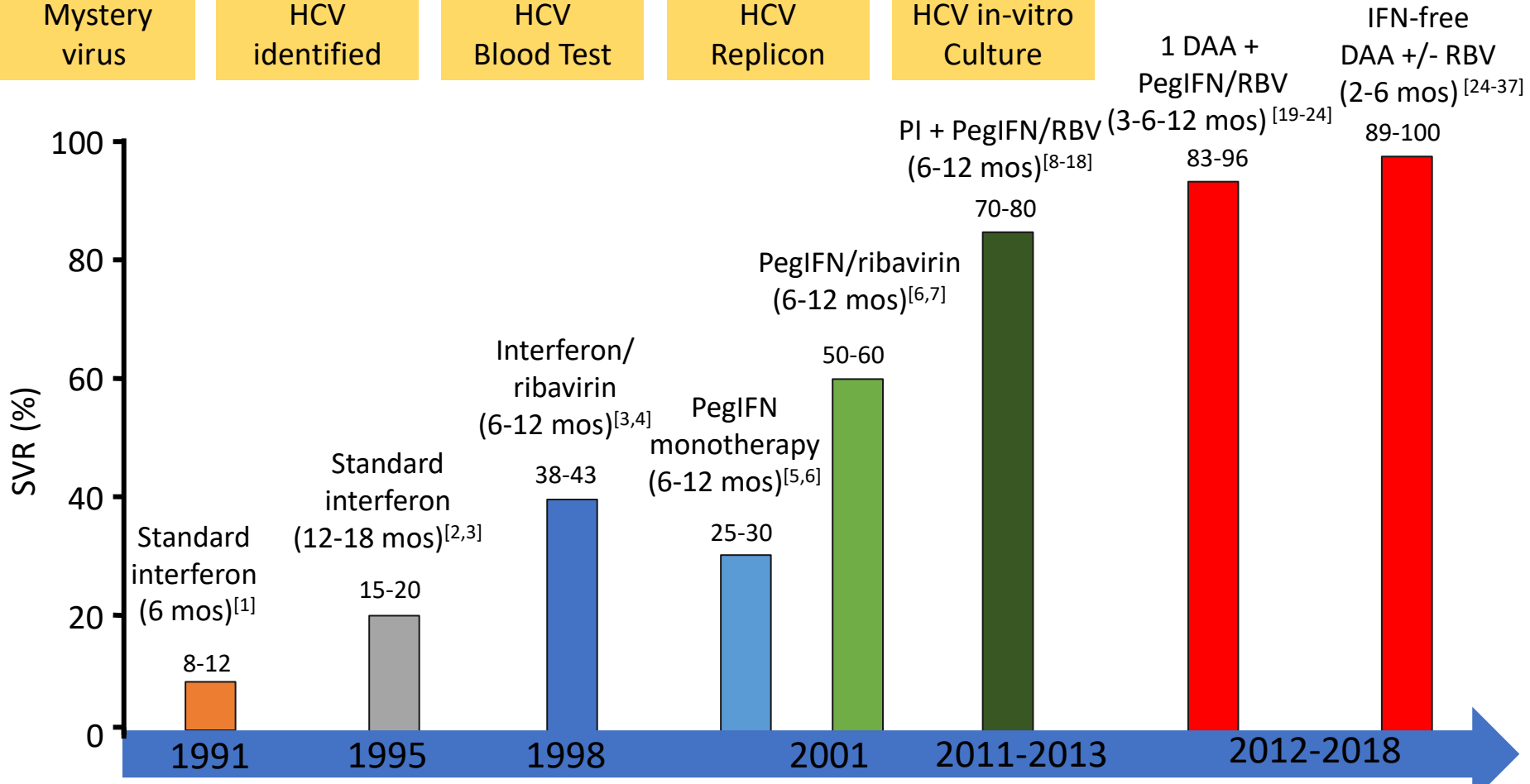
2016: The WHO Global Health Sector established the goal of HCV elimination as a major public health target by 2030

World Health Organization



The standard of care for HCV patients has greatly improved

1974	1989	1992	1999	2005
Mystery virus	HCV identified	HCV Blood Test	HCV Replicon	HCV in-vitro Culture



1. Carithers RL Jr., et al. Hepatology. 1997;26(3 suppl 1):83S-88S. 2. Zeuzem S, et al. N Engl J Med. 2000;343:1666-1672. 3. Poynard T, et al. Lancet. 1998;352:1426-1432. 4. McHutchison JG, et al. N Engl J Med. 1998;339:1485-1492. 5. Lindsay KL, et al. Hepatology. 2001;34:395-403. 6. Fried MW, et al. N Engl J Med. 2002;347:975-982. 7. Manns MP, et al. Lancet. 2001;358:958-965. 8. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 9. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 10. Sherman KE, et al. N Engl J Med. 2011;365:1014-1024. 11. Jacobson IM, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 12. Zeuzem S, et al. Gastroeneterology 2014;146:430-41. 13. Lawitz E, et al. Gastroenterology 2013;144:S-151. 14. Jensen D, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 15. Jacobson I, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, 1-5 November 2013, Washington, DC. 16. Marcellin P, et al. Gastroenterology 2013;145:790-800e3. 17. Bronowicki JP, et al. Antiviral Ther 2013;18:885-93. 18. Manns MP, et al. Hepatology 2012;56:884-93. 19. Hezode C, et al. Hepatology 2012;56:553A- 4A. 20. Dore G, et al. J Hepatol 2013;58:S570-1. 21. Lawitz E, et al. Lancet Infect Dis 2013;13:401-8. 22. Kowdley KV, et al. Lancet 2013;381:2100-7. 23. Lawitz E, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC, 1-5 November 2013. 24. Lawitz E, et al. N Engl J Med 2013;368:1878-87. 25. Jacobson IM, et al. N Engl J Med 2013;368:1867-77. 26. Zeuzem S, et al. N Engl J Med 2014;370:1993-2001. 27. Osinusi A, et al. JAMA 2013;310:804-11. 28. Jacobson IM, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases. Washington, DC, 1-5 November 2013. 29. Sulkowski MS, et al. N Engl J Med 2014;370:211-21. 30. Zeuzem S, et al. N Engl J Med 2014;370:1889-9. 31. Afdhal N, et al. N Engl J Med 2014;370:1483-9. 32. Feld JJ, et al. N Engl J Med 2014;370:1594-603. 33. Zeuzem S, et al. N Engl J Med 2014;370:1604-14. 34. Ferenci P, et al. N Engl J Med 2014;370:1983-9. 35. Poordad F, et al. N Engl J Med 2014;370:1973-82. 36. Lawitz E, et al. 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, 1-5 November 2013. 37. Gane EJ, et al. Gastroenterology 2014;146:736-43e1.

Evolution of Treatment Guidelines: Treatment Is Now Indicated for All Patients

EASL[1] Last updated April 2018	WHO[2] Last updated April 2017	AASLD[3] Last updated September 2017
Treatment is indicated for:		
All treatment-naive and treatment-experienced patients with HCV infection who have no contraindications for treatment*	All adults and children with chronic HCV infection, including PWID	All patients with chronic HCV infection, except those with short life expectancies that cannot be remediated

Practice Guidelines

JOURNAL OF HEPATOLOGY

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

European Association for the Study of the Liver*

* Treatment is generally not recommended in patients with limited life expectancy because of non-liver-related comorbidities.

EASL recommendations on the treatment of hepatitis C 2018. *J Hepatol* 2018; E-pub ahead of print (doi: 10.1016/j.jhep.2018.03.026).
WHO guidelines for the screening, care and treatment of persons with chronic HCV infection. Available at: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1 (accessed March 2018);
AASLD recommendations for testing, managing and treating hepatitis C. Available at: http://www.hcvguidelines.org/full-report-view (accessed March 2018).

I benefici potenziali della SVR

SVR

Familiari, sociali

Economici (diretti e indiretti)

Epatici

Extra-Epatici

Riduzione
- Infiammazione
- Fibrosi
- Cirrosi
- Ipertensione portale: sanguinamemto da varici
- Scompenso: Ascite ecefalopatia
- Epatocarcinoma

Potenziale riduzione
- Crioglobulinemia
- Linfoma B cellulare Non H
- Insufficienza renale
- Linchen Planus, sd Sjogren
- Resistenza insulinica e diabete tipo 2
- Rischio di Ictus e ichemia miocardica
- Fatica e depressione
- Miglioramento funzione neurocognitiva
- Miglioramento del HRQoL e della produzione lavorativa

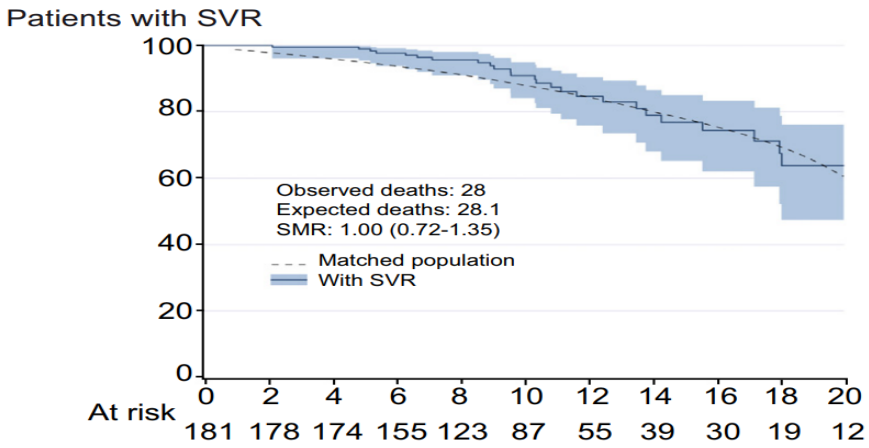
Riduzione della morbilità e mortalità epatica

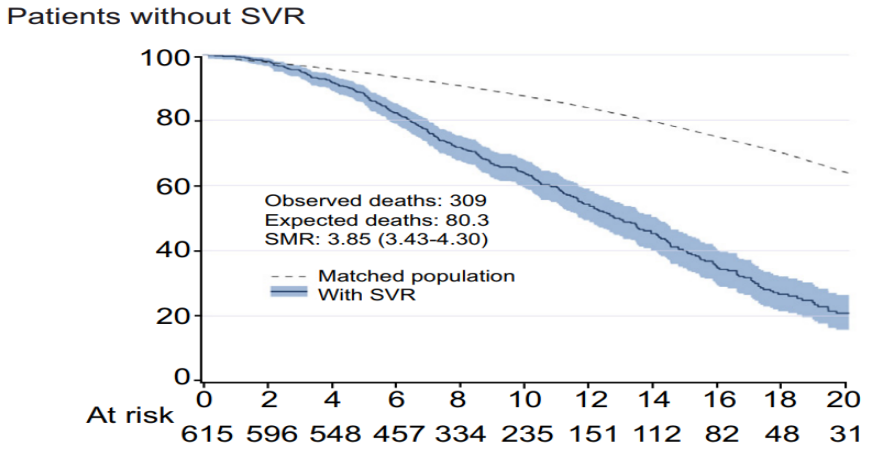
Riduzione della morbilità e mortalità extraepatica

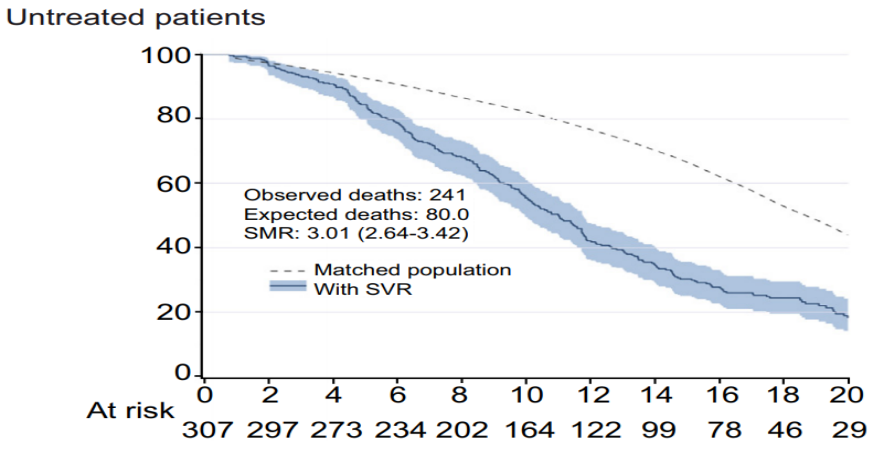
Riduzione di tutte le cause di morte

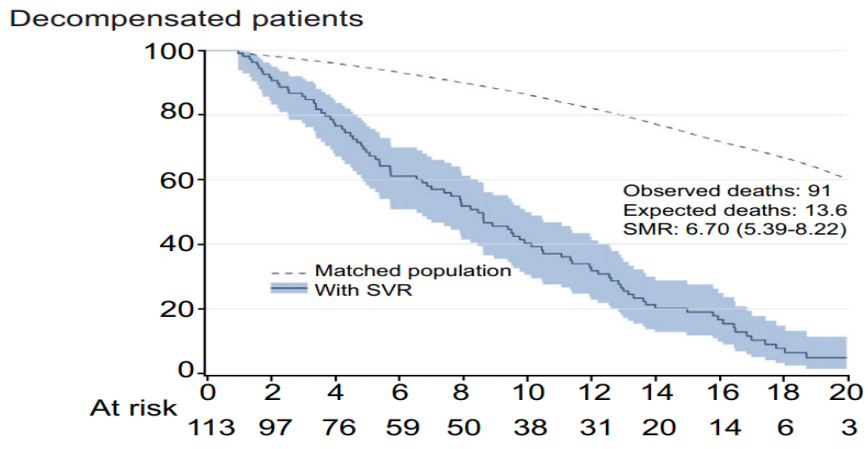
Metwally MA, et al. Gastroenterology 2003; van der Meer AJ, et al. JAMA 2012; Arase Y, et al. Hepatology 2009; Ware JJ, et al. Hepatology 1999

Overall survival in patients with chronic HCV infection and cirrhosis with and without SVR compared with an age- and sex-matched general population without infection









Bruno S, et al. J Hepatol 2016;64:1217–23; EASL CPG HCV. J Hepatol 2018;69:461–511.

Obiettivi del trattamento:

Curare l'infezione HCV reltaa per:

- Prevenire le complicanze epatiche ed extraepatiche relate all'infezione
- Migliorare la qualità di vita e ridurre lo stigma
- Prevenire la trasmissione del virus

Oggi:

- Farmaci pangenotipici
- Alta efficacia (SVR>95%)
- Pressochè assenza di effetti collaterali
- Breve durata di terapia (8-12 settimane)

Goal

Inquadramento del paziente, tutto risolto?

- Valutazione fibrosi/comorbilità/sorveglianza HCC
- Interazioni Farmacologiche
- Popolazioni difficili da trattare Serdp-psichiatrici-carceri
- Riattivazione virologica dopo SVR
- Riattivazioni epatite B in coinfezione
- Cirrosi scompensata/trapianto
- Genotipi difficili
- Insufficienza renale

Management and Treatment of Hepatitis C: Are There Still Unsolved Problems and Unique Populations?

Population	Past	Current State of the Art	Future Perspectives
Decompensated cirrhosis	Unique population due to higher risk for decompensation and side effects during antiviral therapy	Special attention required due to exposure to long-term complications. Negative prognostic factor overall	Not overestimate the impact of SVR on liver function and not overlook the possible persisting need for LT
CKD	Unique population due to: ✓ increased prevalence of CKD in HCV ✓ high prevalence of HCV infection in patients on hemodialysis ✓ increased risk of all-cause mortality	Special attention not required. No need for caution about SOF-based regimens	None
HCV/HIV infection	Historically considered difficult- to-treat due to low SVR rates	No longer a unique population. Attention only to few interactions between DAA and anti-retroviral drugs	None
HCV/HBV infection	Historically considered at risk of developing complications (e.g., cirrhosis and HCC) compared to those with mono-infection.	Relevant risk of HBV re-activation in HBsAg positive during and after DAA therapy	Agreement among international societies regarding the best therapeutic approach
Unusual subtypes	Unknown	Emerging challenge due to the paucity of data	Future studies expected to clarify the best DAA regimen
Prior DAA failure	Unknown	Emerging challenge due to uncertainties regarding the recommended therapeutic approach	Prospective studies expected to validate international societies' recommendations

Abbreviations: CKD, chronic kidney disease; DAA, direct-acting antivirals; HBV, hepatitis B virus; HCC hepatocellular carcinoma; HCV, hepatitis C virus, HIV, human immunodeficiency virus; LT, liver transplantation; SOF, sofosbuvir.

Solitano V Viruses 2021

Inquadramento del paziente, tutto risolto?

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- Genotipi difficili
- Insufficienza renale

Type of NITs available to identify and stage of liver fibrosis

Blood –based tests (serum markers)

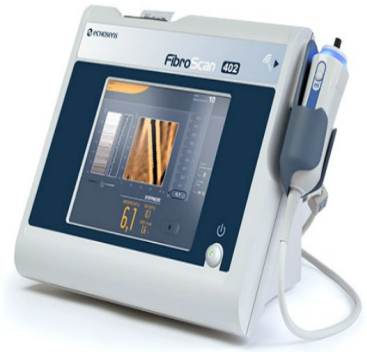
Psysical approach
Liver stiffness measurement (LSM)

AST/ALT ratio
APRI
FIB-4
NFS score

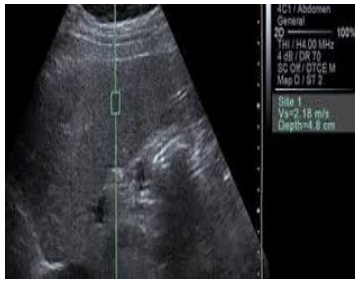
Non Patented

Fibrotest
ELF
FibroMeter
Hepascore

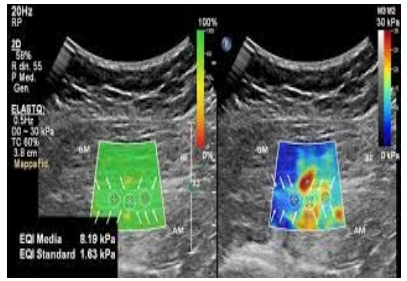
Patented



Transient Elastonography



Point SWE



2D SWE

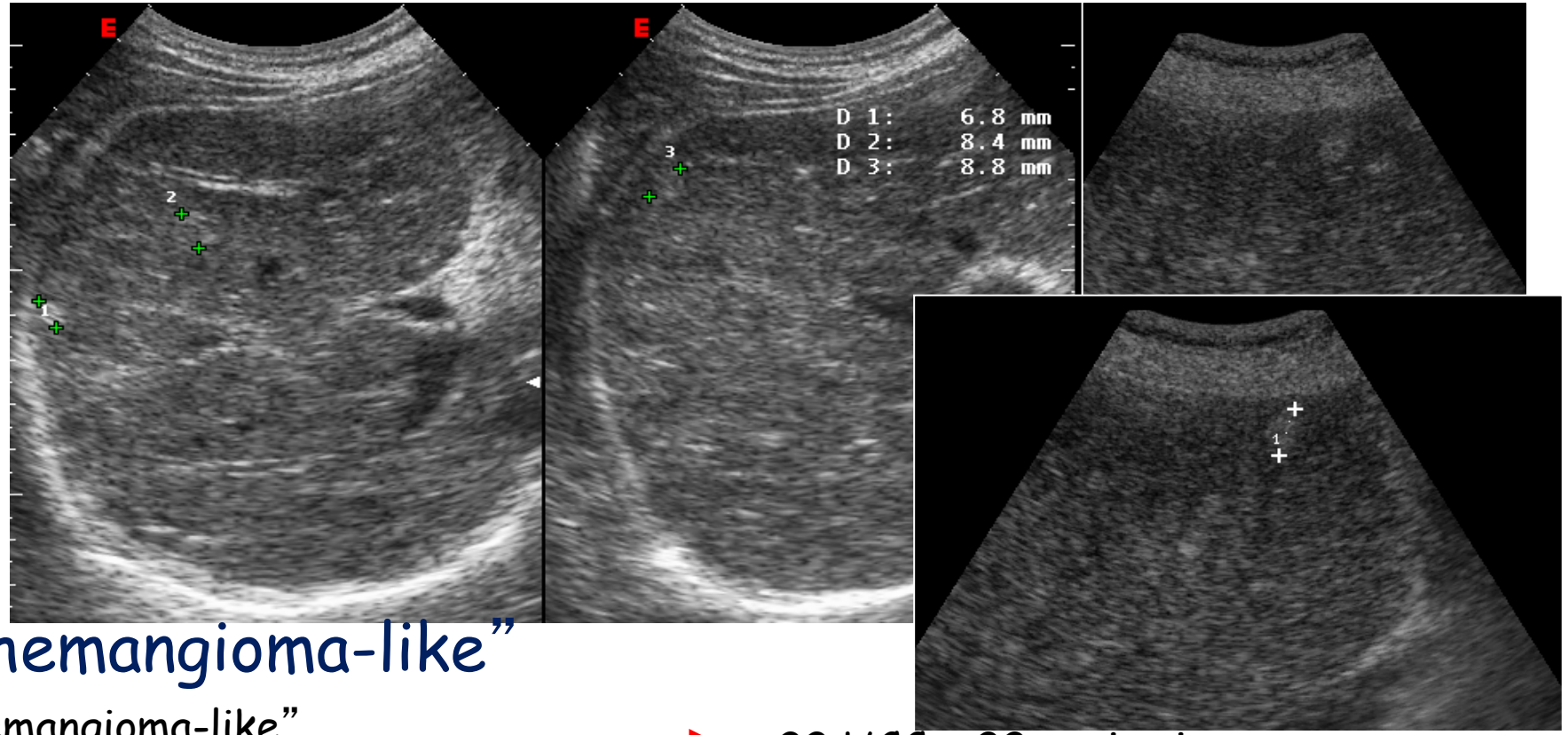
MRE

Easl Clinical Practice Guidelines J Hepatl 2021

Valutazione della fibrosi inziale (Fibroscan 2 d elasto etc)

- Stadia la malattia epatica e consente di pianificare il Follow-up (HCC nei pazienti con F3-F4)
- Attenzione all' ipertransaminasemia che può falsificare la valutazione della fibrosi
- La SVR risolve l'infiammazione e non sempre migliora la fibrosi
- Attenzione alle coomorbilità (alcol, obesità, HCC etc) che possono fare progredire la fibrosi –[valutazione accurate prima di affidare il paziente al medico di famiglia dopo la SVR]

Ruolo dell'Ecografia



Lesioni "hemangioma-like"

44 noduli "hemangioma-like" alla prima osservazione (*casi prevalenti*): → 22 HCC e 22 angiomi

26 noduli "hemangioma-like" durante follow-up (*casi incidenti*): → 22 HCC e 4 HGDN

Caturelli et al, Radiology 2001

Inquadramento del paziente, tutto risolto?

- Valutazione fibrosi/comorbilità/sorveglianza HCC
- Interazioni Farmacologiche
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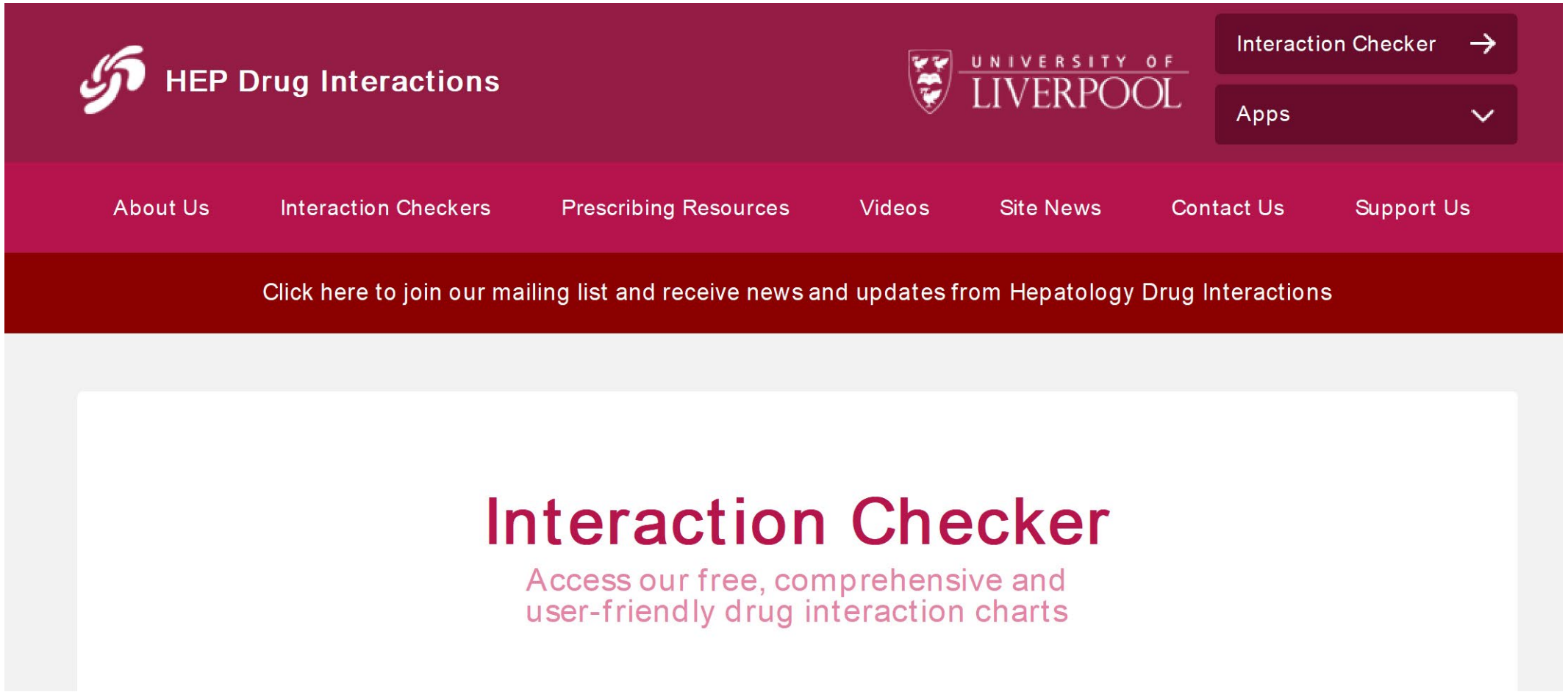
- Riattivazioni epatite B in coinfezione
- Cirrosi scompensata/trapianto
- Genotipi difficili
- Insufficienza renale

Interazioni Farmacologiche



DDIs between HCV DAAs and lipid-lowering drugs

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Atorvastatin	◆	■	■	●	■	●	●
Bezafibrate	◆	◆	◆	◆	◆	◆	
Ezetimibe	◆	◆	◆	■	◆	■	■
Fenofibrate	◆	◆	◆	◆	◆	◆	◆
Fluvastatin	◆	■	■	■	■	●	■
Gemfibrozil	◆	◆	◆	●	■	◆	■
Lovastatin	◆	■	■	●	■	●	●
Pitavastatin	◆	■	■	■	◆	●	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	●	■
Simvastatin	◆	■	■	●	■	●	●

◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be coadministered

EASL CPG HCV. J Hepatol 2018;69:461–511.

DDIs between HCV DAAs and antiplatelets and anticoagulants

	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
Clopidogrel	◆	◆	◆	■	◆	◆	◆
Dabigatran	◆	■	■	■	■	●	●
Ticagrelor	◆	■	■	●	■	■	■
Rivaroxaban	◆	■	■	●	■	■	■
Apixiban	◆	■	■	●	■	■	■
Edoxaban	◆	■	■	■	■	●	■
Warfarin	■	■	■	■	■	■	■

◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be coadministered

EASL CPG HCV. J Hepatol 2018;69:461–511.

Drug-drug interactions between HCV DAAs and antiplatelets and anticoagulants

	G/P	SOF/VEL	SOF/VEL/VOX
Apixaban	▲	▲	▲
Dabigatran	●	■	●
Edoxaban	■	■	●
Rivaroxaban	■	■	■
Warfarin	■	■	■

Variable	Non-cirrhotic N = 168	Cirrhotic N = 36	p-Value[a]
Gender male % (n)	78.0 (131)	83.3 (30)	.475
Mean age years (IQR)	58.0 (47.0–67.0)	48.1 (38.5–56.0)	<.001[b]
Race[c] %(n)			
White/Caucasian	77.4 (130)	66.7 (24)	.060
African American/Black	14.9 (25)	30.6 (11)	
Treatment duration %(n)			
8 weeks	53.0 (89)	2.8 (1)	<.001
12 weeks	44.6 (75)	88.9 (32)	
16 or more weeks	3.4 (4)	8.3 (3)	
DAA treatment regimen			
SOF/VEL	29.2 (49)	47.2 (17)	-[e]
SOF/LDV	29.2 (49)	16.7 (6)	
GLE/PIB	26.2 (44)	13.9 (5)	
EBR/GZR	11.9 (20)	13.9 (5)	
SOF/VEL/VOX	3.0 (5)	2.8 (1)	
SOF/LDV+RBV	0 (0)	5.6 (2)	
SOF/VEL/VOX+RBV	0.6 (1)	0 (0)	
DOAC %(n)			
Rivaroxaban	59.2 (100)	44.4 (16)	.231
Apixaban	37.5 (63)	50.0 (18)	
Edoxaban	3.0 (5)	5.6 (2)	

TABLE 2 Primary and secondary outcomes by cirrhosis status for patients taking direct-acting oral anticoagulants concurrently with direct-acting antivirals for hepatitis C infection.

	Non-cirrhotic (n = 168)	Cirrhotic (n = 36)	Relative risk (95% CI)
Major bleed[a] % (n)	0.60 (1)	5.56 (2)	1.24 (0.56–2.76)
DOAC discontinuation % (n)	2.98 (5)	2.78 (1)	0.93 (0.11–7.75)

...”In conclusion, in this multicenter cohort study of concurrent DAA and DOAC use, mayor bleeding was uncommon and there was no clinically relevant non major bleeding”...

McDaniel K et al - JVH 2022

Inquadramento del paziente, tutto risolto?

- Valutazione fibrosi/comorbilità/sorveglianza HCC
- Interazioni Farmacologiche
- Popolazioni difficili da trattare Serdp-psichiatrici-carceri
- Riattivazione virologica dopo SVR
- Riattivazioni epatite B in coinfezione
- Cirrosi scompensata/trapianto
- Genotipi difficili
- Insufficienza renale

Trattamento del paziente con infezione cronica da HCV afferente ai SerDp

Presa in carico e Approccio Integrato

Fattore Tempo

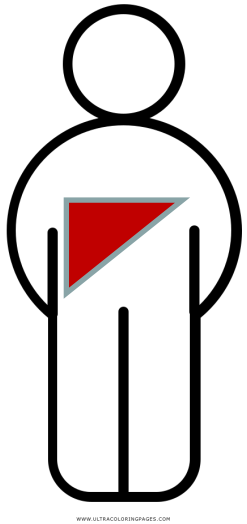
Aderenza

Operatori SerDp

Infermiere Specializz.

Epatologo

Laboratorio



Distribuzione Farmaci

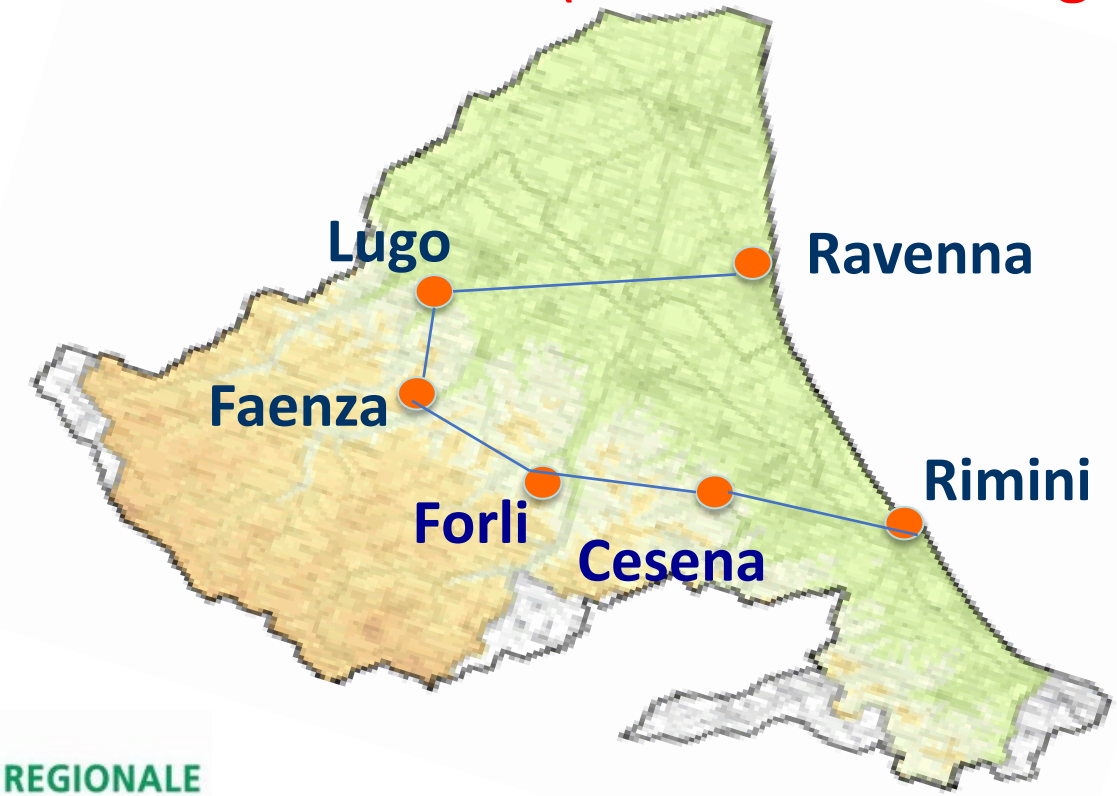
Psichiatra

Imaging Strument. Detect. Fibrosi

Specialisti Diabetologo Cardiologo etc

La Rete Nell' AUSL Romagna SERT e Centri Epatologici

Progetto di Modello Integrato per la gestione dei Pazienti HCV + afferenti ai SERT (obiettivo di Budget 2018)



SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

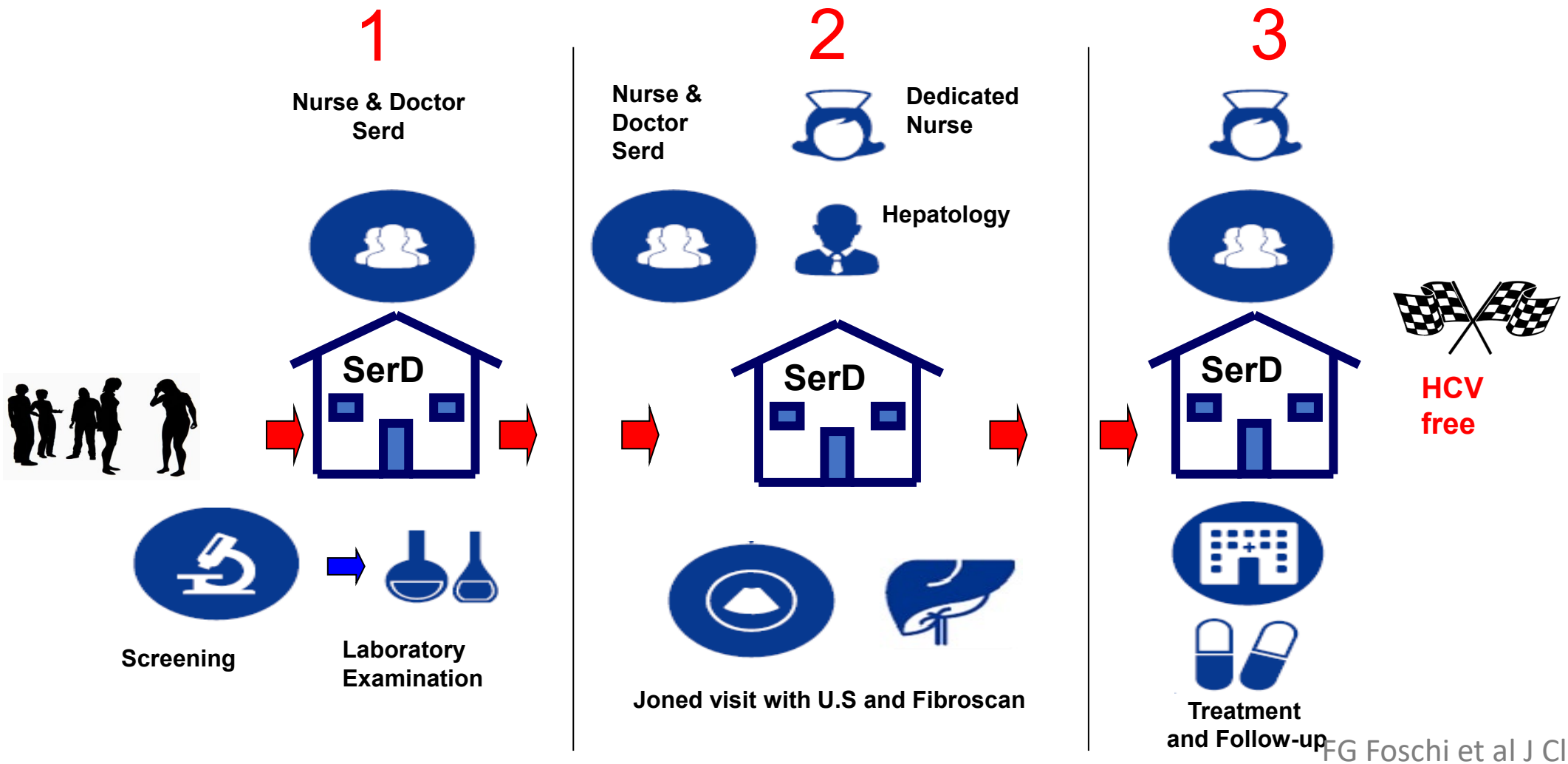
Obiettivi di Budget AUSL Romagna 2018

B1.020		**Percorso Approccio multidisciplinare del paziente hcv+ afferente al SerD**		
	B1.020.01	Numero di meeting multidisciplinare per ambito	>=	6
B1.022		**Percorso insufficienza renale cronica avanzata**		
	B1.022.01	% di pazienti uremici che iniziano la dialisi nell'anno (pazienti incidenti) che giungono adeguatamente preparati al trattamento (fistola artero-venosa o catetere venoso centrale tunnellizzato o catetere peritoneale)	>=	75
	B1.022.02	Pazienti inviati annualmente al Centro Trapianti dagli ambulatori di pre-dialisi per programmi di trapianto da donatore vivente	>=	8
	B1.022.03	Possibilità di accesso nell'ambito dell'ambulatorio di pre-dialisi a percorsi di terapia nutrizionale o dietetica con personale dedicato nelle diverse sedi nefrologiche	>=	95
B1.109		**Percorso Screening Colon Retto**		
	B1.109.01	Indicatore: Proporzione di popolazione bersaglio invitata a partecipare al programma di screening colon rettale.	>=	95

- PDTA :
- Completamento della Formazione:
- Ambulatorio multidisciplinare condiviso arruolamento di almeno 100 pz:
- Progetto di Ricerca con approvazione CE

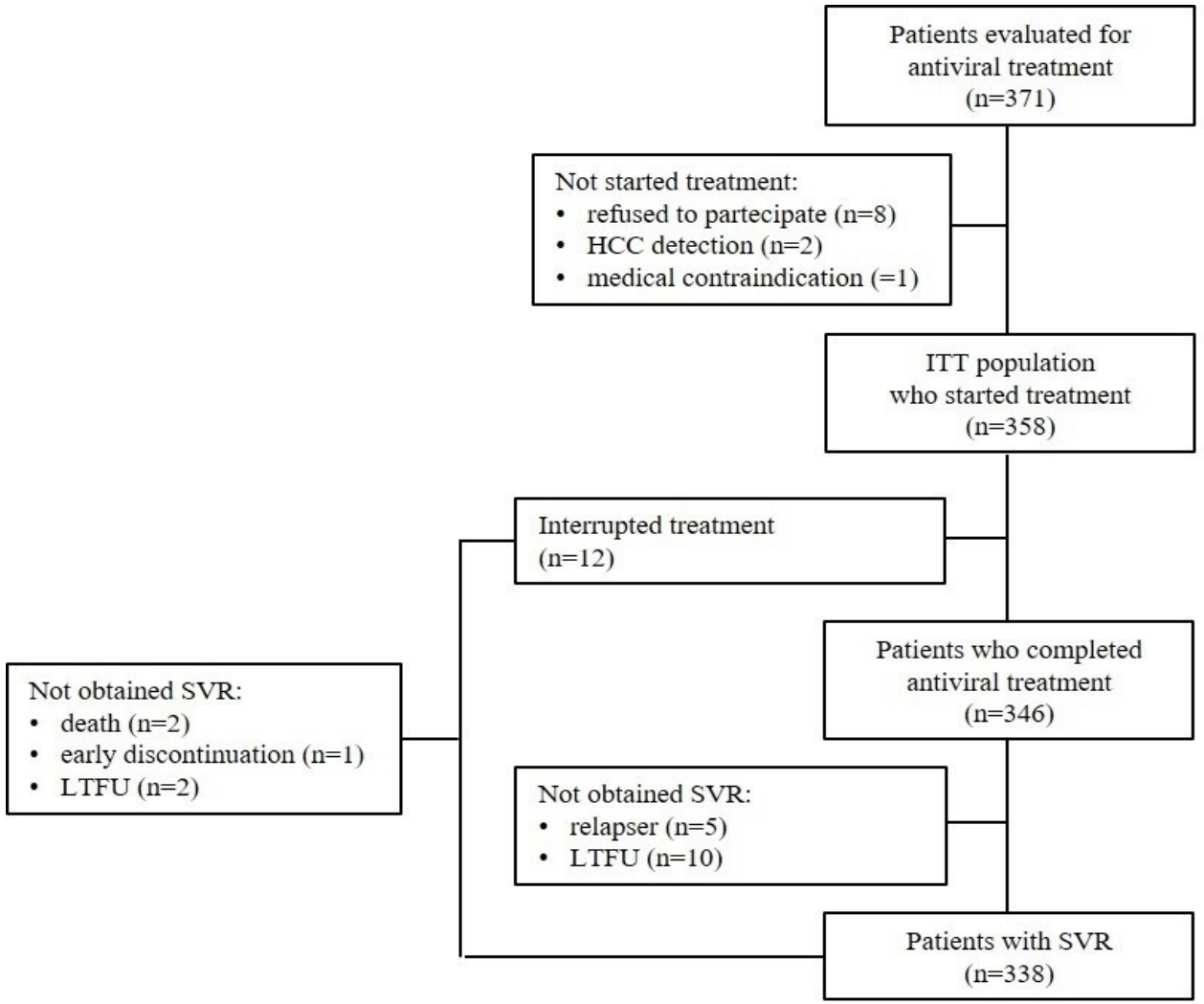
Model of Care for Microelimination of Hepatitis C Virus Infection among People Who Inject Drugs

From Centralizated to Decentralizated Services



FG Foschi et al J Clin. Med. 2021

Model of Care for Microelimination of Hepatitis C Virus Infection among People Who Inject Drugs



FG Foschi et al J Clin. Med. 2021

Characteristics of PWID with HCV Chronic Hepatitis

Characteristics	All patients (n=358)
Age (years)	49 (18-69)
Birth cohort:	
• <1965	87 (24.3%)
• 1965–1974	171 (47.8%)
• ≥1975	100 (27.9%)
Male sex	297 (83%)
BMI ≥25	179 (50%)
Advanced fibrosis	176 (49.1%)
Fibrosis stage:	
• F0-1	124 (34.6%)
• F2	58 (16.2%)
• F3	66 (18.4%)
• F4	110 (30.7%)
Genotype:	
• 1a	149 (41.1%)
• 1b	21 (5.9%)
• 2	2 (0.6%)
• 3	142 (39.7%)
• 4	44 (12.3%)
HCV treatment naive	281 (78.5%)

FG Foschi et al J Clin. Med. 2021

Characteristics of PWID with HCV Chronic Hepatitis

HBV coinfection	4 (1.1%)
Diabetes	20 (5.6%)
Arterial hypertension	41 (11.5%)
Psychiatric disorders	140 (39.1%)
Psychiatric treatment:	
• benzodiazepine	104 (29.1%)
• antipsychotics	72 (20.1%)
• antidepressants	34 (9.5%)
• valproic acid	12 (3.4%)
Any alcohol use	259 (72.3%)
Current tobacco use	296 (82.7%)
OST prescription:	
• methadone	204 (57%)
• buprenorphine	43 (12%)
Drug use status:	
• former	284 (79.3%)
• recent	74 (20.7%)

FG Foschi et al J Clin. Med. 2021

Factors associated with failure treatment (according ITT analysis) to direct acting antiviral drug combinations.

				Multivariate analysis	
Variable	**n/N**	**SVR**	**p**	**Odds ratio (95% IC)**	**p**
Age:			0.661		
• <50 years	203/216	94%			
• ≥50 years	135/142	95.1%			
Sex:			0.803		
• male	280/297	94.3%			
• female	58/61	95.1%			
Stage of fibrosis:			0.939		
• mild/moderate	172/182	94.5%			
• advanced/ cirrhosis	166/176	94.3%			
HCV genotype:			0.331		
• genotype 3	132/142	93%			
• others genotypes	206/216	95.4%			
Previous HCV treatment:	265/281	94.3%	0.866		
• naive	73/77	94.8%			
• experienced					
Alcohol use:			0.431		
• yes	243/259	93.8%			
• no	95/99	96%			
OST			0.273		
• yes	231/247	93.5%			
• no	107/111	96.4%			
Recent drug use:			0.028		
• yes	66/74	89.2%		2.747 (1.080-6.992)	0.034
• no	272/284	95.8%			
Psychiatric disorders:			0.072		
• yes	136/140	97.1%			
• no	202/218	92.7%			

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Modello Integrato (multidisciplinare)

- Facilitazione alla presa in carico del paziente
- Integrazione dei Professionisti
- Indicato in tutti i consumatori di sostanze (anche gli attivi)
- Riduzione dei drop out, migliora l'aderenza
- Facilità accesso alla stadiazione / motivazione della cure
  - Personale dedicato medico del SERT- Infermiera del Sert, Infermiera motivata dell'Ambulatorio epatologico/infettivologico
  - Valutazione epatopatia fibroscan, malattie extraepatiche , ecografia specialistica
  - Cura delle coomorbilità sovrappeso,alcol, diabete etc

Open access

BMJ Open

Nurse-led clinic for patients with liver cirrhosis—effects on health-related quality of life: study protocol of a pragmatic multicentre randomised controlled trial

Maria Hjorth,[1,2] Daniel Sjöberg,[1] Anncarin Svanberg,[2,3,4] Elenor Kaminsky,[3] Sophie Langenskiöld,[3] Fredrik Rorsman[2]

BMJ Open 2018;**8**:e023064. doi:10.1136/bmjopen-2018-023064

REVIEW ARTICLE

CHANEY AND YATACO

The Emerging Role of Nurse Practitioners and Physician Assistants in Liver Transplantation

Amanda J. Chaney and Maria L. Yataco

Division of Transplant Medicine, Mayo Clinic, Jacksonville, FL

Liver Transplantation 25 1105–1109 2019 AASLD.

Preparazione del Paziente al trattamento: Ruolo dell'Infermiere specializzato

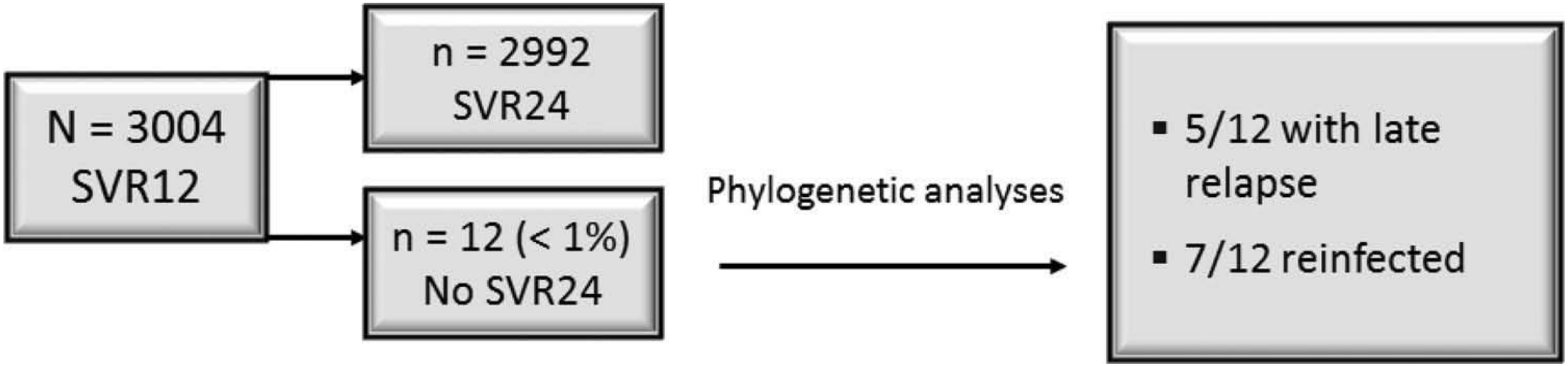
COUNSELING INFERMIERISTICO Relazione d'aiuto basata sull'ascolto e sulla comunicazione che l'infermiere utilizza unendo le capacità comunicative e le conoscenze tecniche specifiche.

- **Approccio Personalizzato**
- **Incrementa la CONSAPEVOLEZZA**
- **Migliora l'autonomia**
- **Addestra i Care giver**
- **Punto di riferimento facilmente accessibile**
- **Migliora ADERENZA**
- **Facilitazione dei controlli durante la terapia e il Follow-up**

Inquadramento del paziente, tutto risolto?

- Valutazione fibrosi/comorbilità/sorveglianza HCC
- Interazioni Farmacologiche
- Popolazioni difficili da trattare Serdp-psichiatrici-carceri
- Riattivazione virologica dopo SVR
- Riattivazioni epatite B in coinfezione
- Cirrosi scompensata/trapianto
- Genotipi difficili
- Insufficienza renale

Late relapse beyond SVR12 with DAA therapy. Is not common but it can occur



- Incomplete/sub-obtimal treatment
- Immunosuppression
- Cirrhosis
- Coinfenction

Recommendend cheking for SVR at 48 week, in addiction to 12 week after EOT

Sarrazin C et al Clin Inf Dis 2017- Massoud O Expert Review Gastroenterol and Hepatol 2020

Inquadramento del paziente, tutto risolto?

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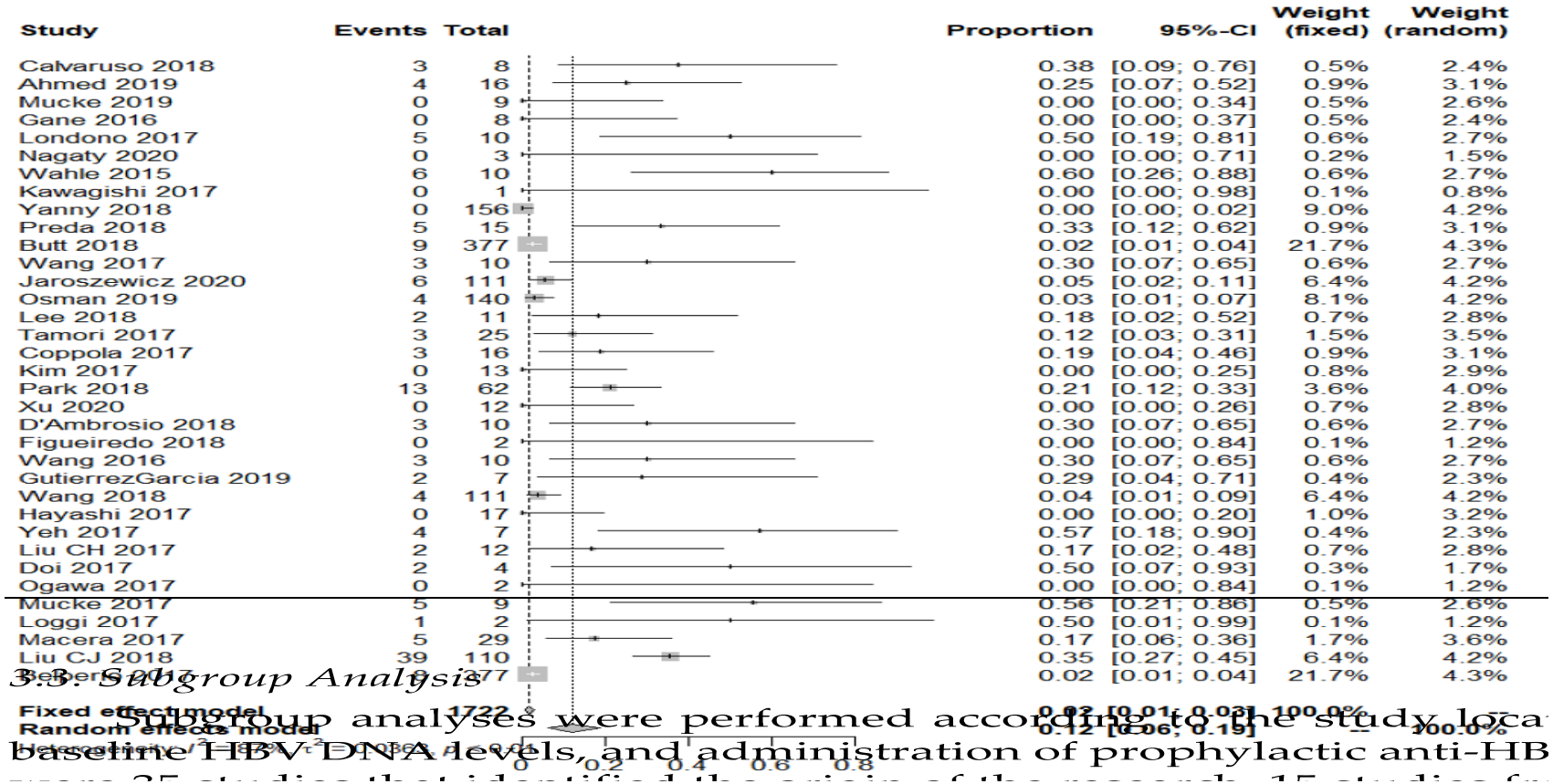
- Insufficienza renale

Overall risk of HBV reactivation



Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Calvaruso 2018	3	8	0.38	[0.09; 0.76]	0.5%	2.4%
Ahmed 2019	4	16	0.25	[0.07; 0.52]	0.9%	3.1%
Mucke 2019	0	9	0.00	[0.00; 0.34]	0.5%	2.6%
Gane 2016	0	8	0.00	[0.00; 0.37]	0.5%	2.4%
Londono 2017	5	10	0.50	[0.19; 0.81]	0.6%	2.7%
Nagaty 2020	0	3	0.00	[0.00; 0.71]	0.2%	1.5%
Wahle 2015	6	10	0.60	[0.26; 0.88]	0.6%	2.7%
Kawagishi 2017	0	1	0.00	[0.00; 0.98]	0.1%	0.8%
Yanny 2018	0	156	0.00	[0.00; 0.02]	9.0%	4.2%
Preda 2018	5	15	0.33	[0.12; 0.62]	0.9%	3.1%
Butt 2018	9	377	0.02	[0.01; 0.04]	21.7%	4.3%
Wang 2017	3	10	0.30	[0.07; 0.65]	0.6%	2.7%
Jaroszewicz 2020	6	111	0.05	[0.02; 0.11]	6.4%	4.2%
Osman 2019	4	140	0.03	[0.01; 0.07]	8.1%	4.2%
Lee 2018	2	11	0.18	[0.02; 0.52]	0.7%	2.8%
Tamori 2017	3	25	0.12	[0.03; 0.31]	1.5%	3.5%
Coppola 2017	3	16	0.19	[0.04; 0.46]	0.9%	3.1%
Kim 2017	0	13	0.00	[0.00; 0.25]	0.8%	2.9%
Park 2018	13	62	0.21	[0.12; 0.33]	3.6%	4.0%
Xu 2020	0	12	0.00	[0.00; 0.26]	0.7%	2.8%
D'Ambrosio 2018	3	10	0.30	[0.07; 0.65]	0.6%	2.7%
Figueiredo 2018	0	2	0.00	[0.00; 0.84]	0.1%	1.2%
Wang 2016	3	10	0.30	[0.07; 0.65]	0.6%	2.7%
GutierrezGarcia 2019	2	7	0.29	[0.04; 0.71]	0.4%	2.3%
Wang 2018	4	111	0.04	[0.01; 0.09]	6.4%	4.2%
Hayashi 2017	0	17	0.00	[0.00; 0.20]	1.0%	3.2%
Yeh 2017	4	7	0.57	[0.18; 0.90]	0.4%	2.3%
Liu CH 2017	2	12	0.17	[0.02; 0.48]	0.7%	2.8%
Doi 2017	2	4	0.50	[0.07; 0.93]	0.3%	1.7%
Ogawa 2017	0	2	0.00	[0.00; 0.84]	0.1%	1.2%
Mucke 2017	5	9	0.56	[0.21; 0.86]	0.5%	2.6%
Loggi 2017	1	2	0.50	[0.01; 0.99]	0.1%	1.2%
Macera 2017	5	29	0.17	[0.06; 0.36]	1.7%	3.6%
Liu CJ 2018	39	110	0.35	[0.27; 0.45]	6.4%	4.2%
Reberg 2017	9	377	0.02	[0.01; 0.04]	21.7%	4.3%
Fixed effect model	**1722**		**0.03**	**[0.01; 0.03]**	**100.0%**	
Random effects model			**0.12**	**[0.06; 0.19]**		**100.0%**

Heterogeneity: I^2 = 83%, τ^2 = 0.0136, p < 0.01

0 0.2 0.4 0.6 0.8

3.3. Subgroup Analysis

Subgroup analyses were performed according to the study loca
baseline HBV DNA levels, and administration of prophylactic anti-HB

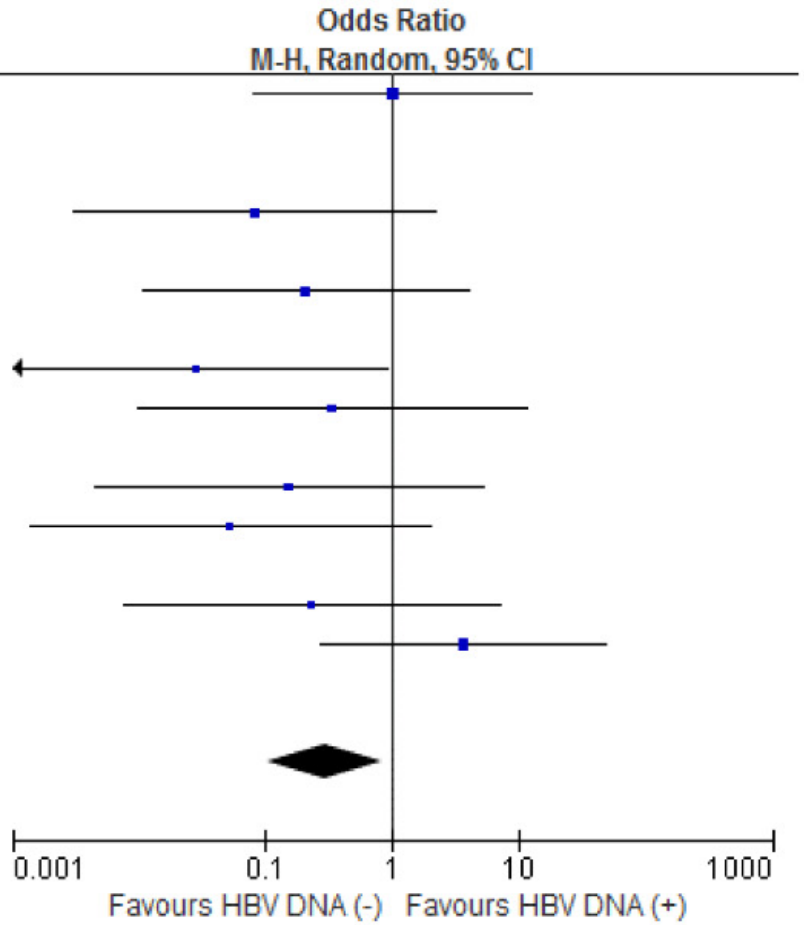
In the 35 studies that reported data on HBsAg-positive patients receiving DAA therapy, the pooled HBV reactivation rate was 12% (95% confidence interval (CI) 6–19)

J H Oh et al J Med 2022

The risk of HBV reactivation according to baseline HBV DNA.

Study or Subgroup	HBV DNA (-) Events	Total	HBV DNA (+) Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Wahle 2015	3	5	3	5	17.0%	1.00 [0.08, 12.56]	2015
Gane 2016	0	4	0	4		Not estimable	2016
Yeh 2017	0	4	0	3		Not estimable	2017
Belperio 2017	0	38	1	10	10.2%	0.08 [0.00, 2.18]	2017
Kawagishi 2017	0	0	0	0		Not estimable	2017
Liu 2017	0	37	4	74	12.6%	0.21 [0.01, 3.98]	2017
Londono 2017	0	4	0	2		Not estimable	2017
Macera 2017	1	11	2	2	9.0%	0.03 [0.00, 0.93]	2017
Mucke 2017	0	3	1	4	8.8%	0.33 [0.01, 11.34]	2017
Wang 2018	0	0	3	10		Not estimable	2018
Calvaruso 2018	2	7	1	1	8.7%	0.15 [0.00, 5.18]	2018
Lee 2018	1	10	1	1	8.3%	0.05 [0.00, 1.99]	2018
Liu 2018	0	5	0	7		Not estimable	2018
Preda 2018	0	6	1	5	9.3%	0.23 [0.01, 7.05]	2018
Ahmed 2019	2	8	1	12	16.2%	3.67 [0.27, 49.29]	2019
Mucke 2019	0	9	0	0		Not estimable	2019
Total (95% CI)		**151**		**140**	**100.0%**	**0.30 [0.11, 0.86]**	
Total events	9		18				

Heterogeneity: Tau² = 0.00; Chi² = 7.90, df = 8 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)



Patients with undetectable HBV DNA showed a decreased risk of reactivation than those with detectable HBV DNA (≥20 IU/mL) (OR 0.27, 95% CI 0.07–1.01, I2 = 0%)

J H Oh et al J Med 2022

HBV Reactivaction mechanisms

- HCV core protein (NS2 and NS5a) has an inhibitory effect on HBV replication
- HCV infection activates the host immune system
- The side effects of the DAA therapy were similar to immunosuppressants
- Two viruses compete for a limited replicative space
- Other

Key message

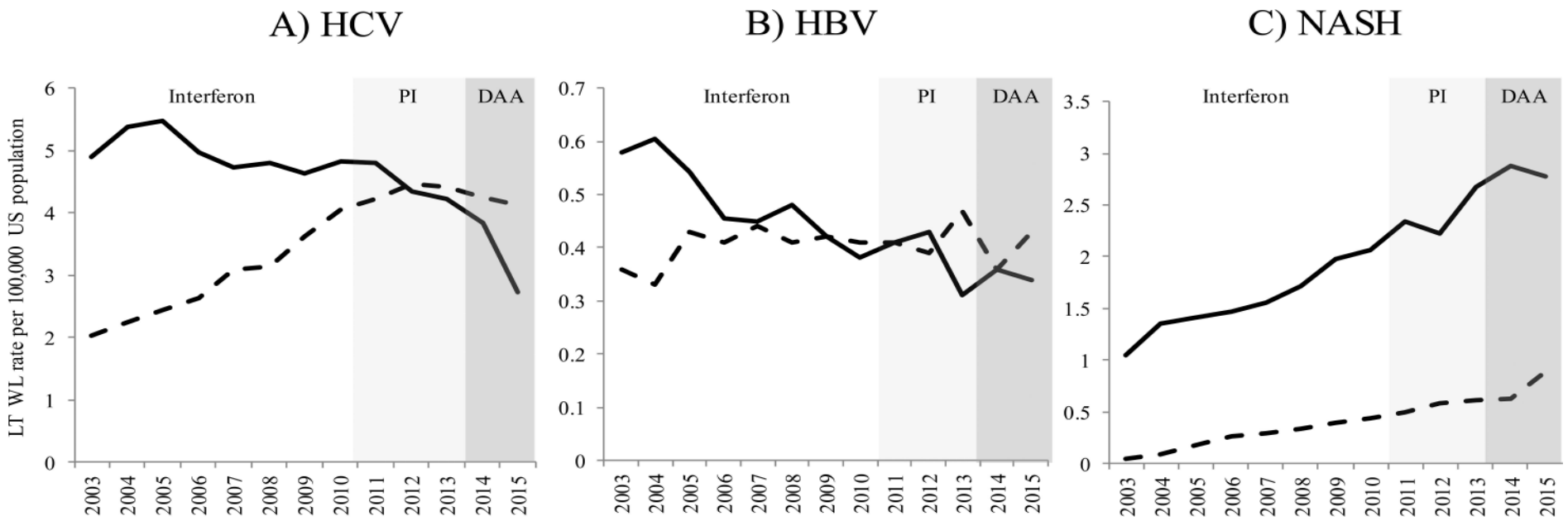
- HBV testing should be done in evaluation of the HCV patients
- HBV reactivation-related hepatitis was significantly lower in patients with undetectable HBV DNA
- Patients with detectable HBV DNA levels had a greater risk of reactivation than those with lower HBV DNA levels.
- Patients with detectable HBV DNA or impaired liver function require antiviral therapy

Inquadramento del paziente, tutto risolto?

- Valutazione fibrosi/comorbilità/sorveglianza HCC
- Interazioni Farmacologiche
- Popolazioni difficili da trattare Serdp-psichiatrici-carceri
- Riattivazione virologica dopo SVR
- Riattivazioni epatite B in coinfezione
- Cirrosi scompensata/trapianto
- Genotipi difficili
- Insufficienza renale

Reduction in Liver Transplant Wait-Listing in the Era of Direct Acting Anti-Viral Therapy

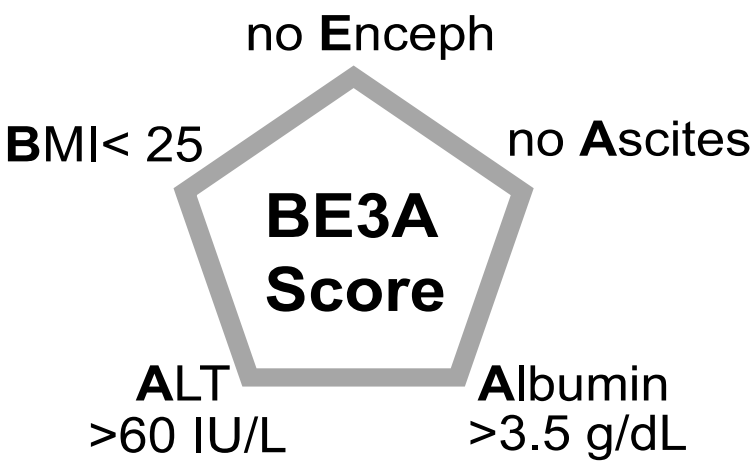
Annual standardized incidence rates (ASIR) of LT wait-listing per 100,000 US population by etiology of liver disease and indication for wait-listing.

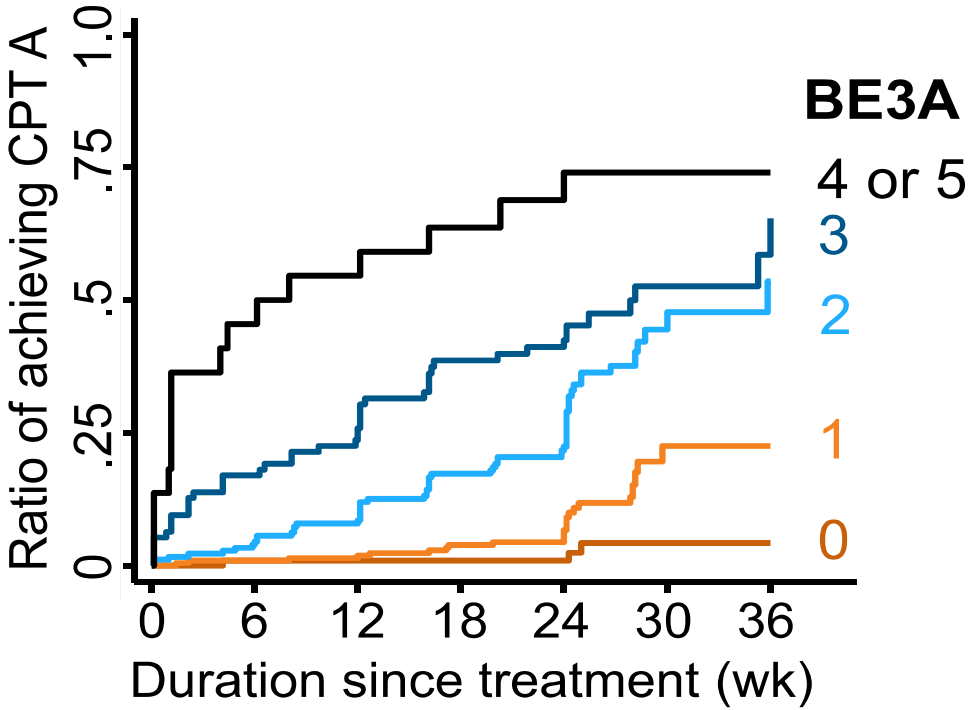


Flemming. JA et al J Hepatol 2017

Baseline Factors Associated With Improvements in Decompensated Cirrhosis After Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection

(502 of CPT class B and 120 of CPT class C)





Patients with a BE3A score of 4 have a 75% chance of recovering to CTP class A after DAA treatment.

El-Sherif = et al Gastroenterol 2018

Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity

Survival in patients with SVR vs. no SVR. (A-C) Child-Pugh A cirrhosis; (D-F) Child Pugh B/C cirrhosis. Statistical significance was assessed with Log-rank test. HCC, hepatocellular carcinoma; LT, liver transplantation; SVR, sustained virological response

Krassenburgv AP et al J Hepatol 2021

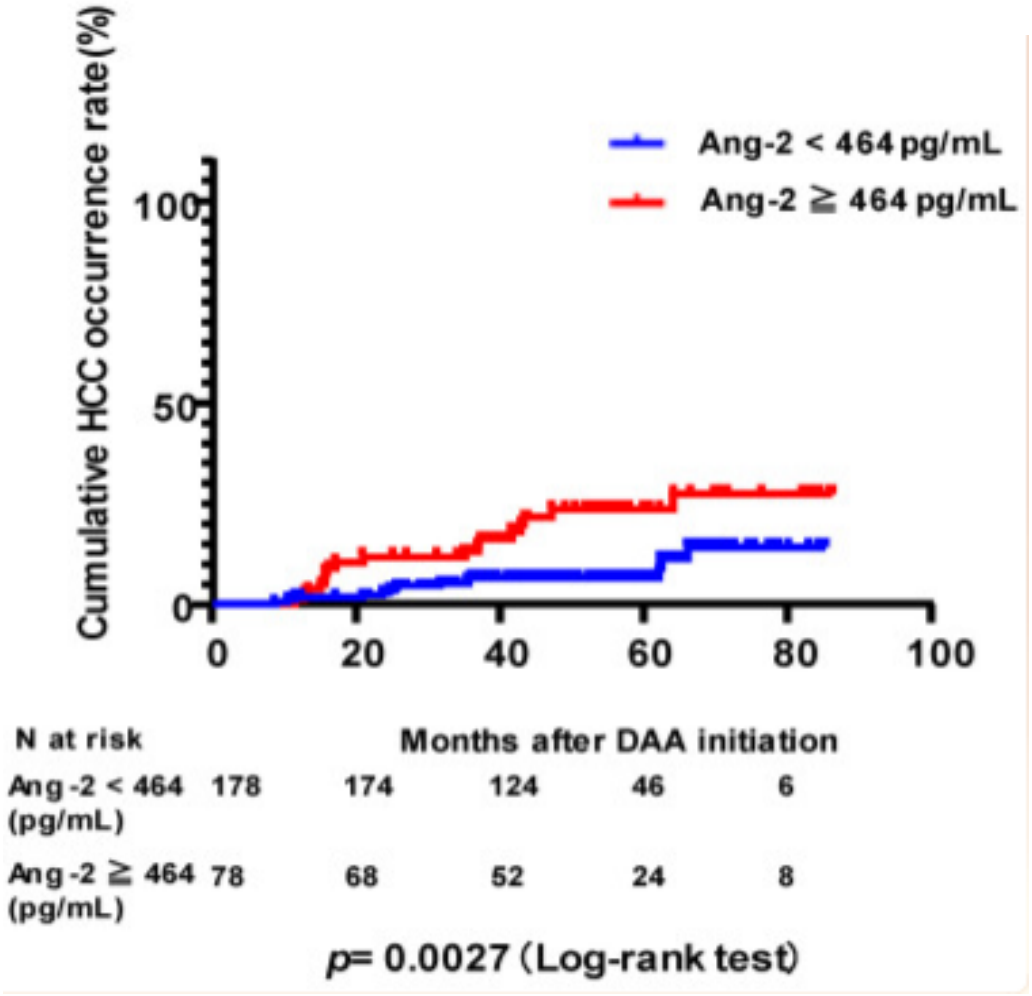
Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity

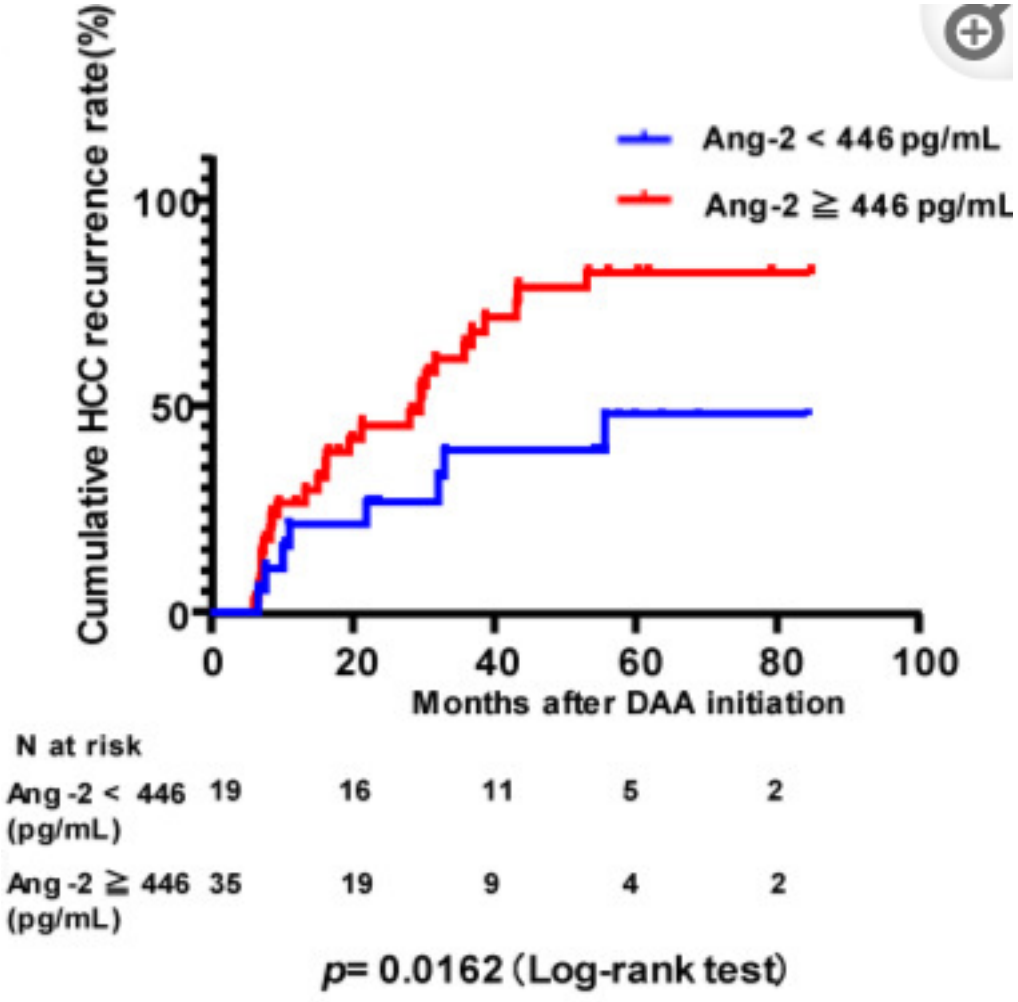
Survival in patients with SVR vs. no SVR. (A-C) Child-Pugh A cirrhosis; (D-F) Child Pugh B/C cirrhosis. Statistical significance was assessed with Log-rank test. HCC, hepatocellular carcinoma; LT, liver transplantation; SVR, sustained virological response

Krassenburgv AP et al J Hepatol 2021

Serum Angiopoietin-2 Predicts the Occurrence and Recurrence of Hepatocellular Carcinoma after Direct-Acting Antiviral Therapy for Hepatitis C

310 HCV-infected patients treated with DAAs





Kawagishi N et al Viruses 2023


Ευχαριστώ
謝謝
شكرا لك
감사합니다
Merci
Gracias
Cnacubo
Thank you
Danke
شكرا
감사합니다
Merci
谢谢
Danke
謝謝
متشكرم
Cnacubo
Dziękuję
Gracias
Obrigado