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ORIGINAL ARTICLE

Advanced liver disease outcomes after hepatitis C eradication by human immunodeficiency virus infection in PITER cohort

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BMC Infectious Diseases

RESEARCH Open Access

Liver function following hepatitis C virus eradication by direct acting antivirals in patients with liver cirrhosis: data from the PITER cohort

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AIM

We evaluated the sociodemographic and clinical profile of HCV/HIV coinfected versus HCV monoinfected patients in the PITER cohort, with the final goal to prospectively evaluate the clinical impact of DAA treatment in patients with progressive/severe liver disease according to HIV coinfection status.

STUDY POPULATION

- **Study population:** Consecutively patients enrolled in the PITER cohort from April 2014 to June 2019, including HCV/HIV coinfected patients and HCV monoinfected patients with known HIV negative status, with pre-treatment diagnosis of liver cirrhosis who had achieved SVR12 to IFN-free DAA regimens.

- **Inclusion criteria:**
  -Patients with at least 12-weeks follow-up after end of DAA treatment

- **Exclusion criteria:**
  -Liver transplantation
  -History of decompensated cirrhosis

Baseline characteristics of the study population

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Quantitative variables	HIV/HCV coinfected (N=93* - SVR 94.9%) Median (Range)	HCV monoinfected (N=1109*- SVR 94.8%) Median (Range)	p**
FU time since EOT (months)	26.7 (6.0 - 44.6)	24.6 (6.8 - 47.3)	0.7595
Age (years)	52 (36 - 77)	64 (23 - 86)	**< 0.001**
ALT (IU/L)	65.5 (11.0 - 268.0)	76.5 (10.0 - 797.0)	**0.0365**
AST (IU/L)	63.5 (23.0 - 371.0)	71.0 (13.0 - 652.0)	0.3184
Platelets/µL	115000 (29000 - 262000)	121000 (15000 - 510000)	0.2817
Albumin (g/dL)	4.0 (3.0 - 5.1)	4.0 (2.1 - 7.3)	0.9712
Bilirubin (mg/dL)	0.8 (0.3 - 7.0)	0.9 (0.2 - 15.5)	0.6845
INR	1.1 (0.9 - 1.5)	1.1 (0.6 - 5.0)	0.6735

- **Data from 93 HIV/HCV coinfected patients (79.6% males) and 1109 HCV monoinfected patients (57.9% males), were evaluated.**
- **Genotype 1a and 3 were prevalent in coinfected patients whereas about half of the monoinfected patients were infected by HCV genotype 1b.**
- **Coinfected patients were observed to have a significantly younger age (median age of 52 vs 64 years) and increased liver disease severity in terms of Child-Pugh class distribution, compared to HCV monoinfected patients.**

		HIV/HCV coinfected N. (%)	HCV monoinfected N. (%)	p*
Sex	Male	74 (79.6)	642 (57.9)	**< 0.001**
	Female	19 (20.4)	467 (42.1)	
BMI	Underweight	5 (5.4)	11 (1.0)	**< 0.001**
	Normal	59 (63.4)	463 (41.8)	
	Overweight	22 (23.7)	489 (44.1)	
	Obese	7 (7.5)	145 (13.1)	
Alcohol use	Never	43 (51.2)	716 (65.9)	**< 0.001**
	Current	25 (29.8)	109 (10.0)	
	Past	16 (19.1)	261 (24.0)	
Genotype	1 (Non subtyped)	5(5.4)	31 (2.8)	**< 0.001**
	1a	29(31.2)	157 (14.2)	
	1b	13(14.0)	592 (53.4)	
	2	4(4.3)	156 (14.1)	
	3	25 (26.9)	104 (9.4)	
	4-5	17 (18.3)	69 (6.2)	
Diabetes	Yes	11 (11.8)	220 (19.8)	0.060
	No	82 (88.2)	889 (80.2)	
Anti-HBc+	Yes	42 (45.2)	248 (22.4)	**< 0.001**
	No	51 (54.8)	861 (77.6)	
HBsAg+	Yes	3 (3.2)	14 (1.3)	0.124
	No	90 (96.8)	1095 (98.7)	
Previous	Yes	26 (28.0)	375 (33.8)	0.250
	No	67 (72.0)	734 (66.2)	
HCC	Yes	1 (1.1)	55 (5.0)	0.088
	No	92 (98.9)	1054 (95.0)	
Child-pugh	A	50 (83.3)	940 (96.6)	**< 0.001**
	B	10 (16.7)	33 (3.4)	

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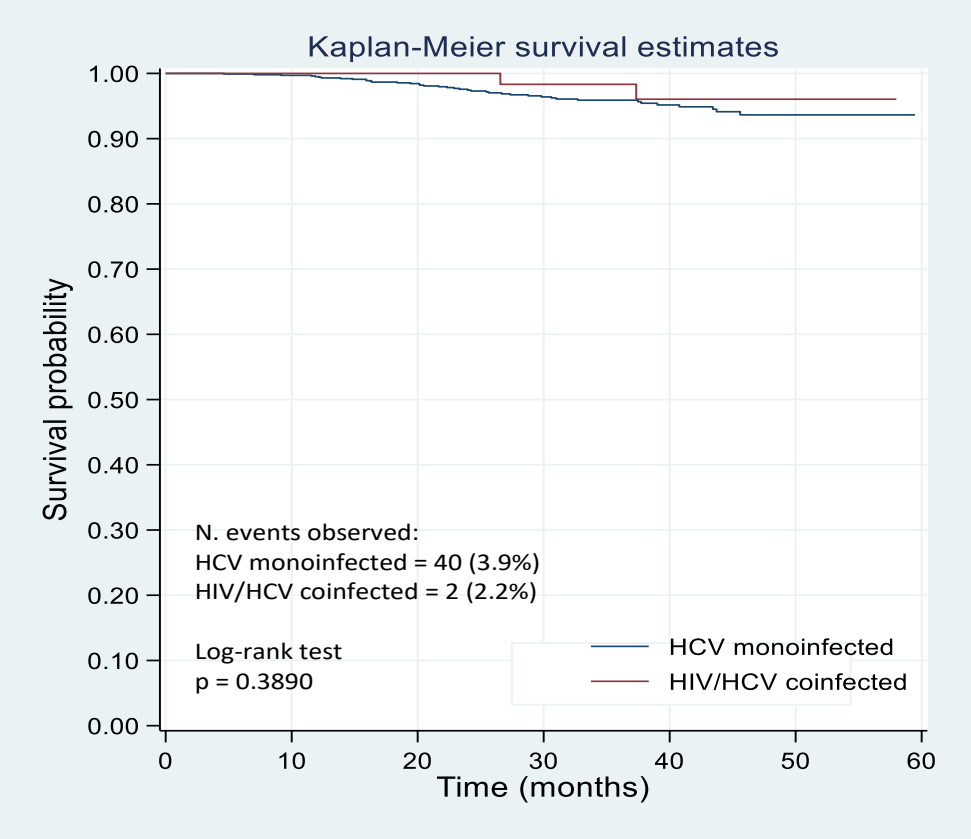
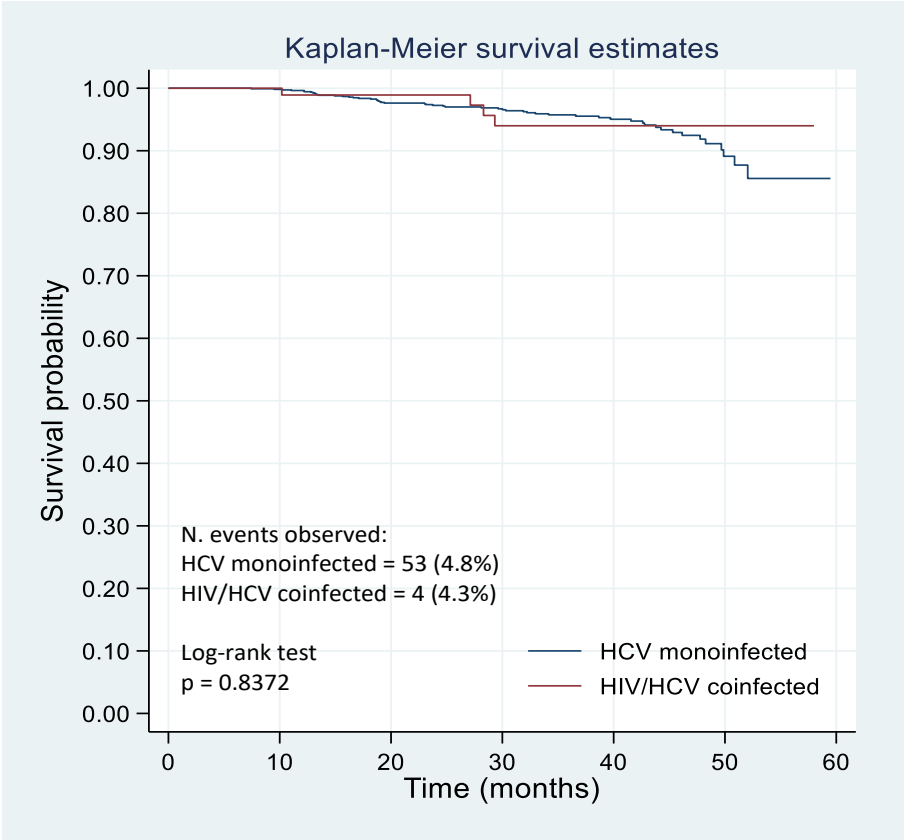
Liver related outcomes following viral eradication



Kaplan-Meier curves for *de novo* HCC occurrence by HCV monoinfected and HIV/HCV coinfected groups



Kaplan-Meier curves for *decompensating event* by HCV monoinfected and HIV/HCV coinfected groups

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Predictors of clinical outcomes following SVR12

Variables associated with *de-novo* HCC occurrence

Baseline factors	Crude HR (95% CI)	Adjusted HR (95% CI)
HIV infection	0.54 (0.13 - 2.24)	0.60 (0.08 4.77)
Age (increasing years)	**1.06 (1.03 - 1.10)**	**1.08 (1.04 - 1.13)**
Sex (ref. female)	**2.68 (1.28 - 5.60)**	**2.76 (1.28 - 5.96)**
BMI: overweight/obese (ref. under-normalweight)	1.07 (0.58 - 1.98)	
Current alcohol use (ref. never) Past alcohol use (ref. never)	1.73 (0.70 - 4.32) **2.13 (1.09 - 4.16)**	
ALT (increasing IU/L)	1.00 (0.99 - 1.00)	
AST (increasing IU/L)	1.00 (0.99 - 1.01)	
Platelets (ref. >100,000/µL)	1.50 (0.81 - 2.79)	
Albumin (decreasing g/dL)	**4.53 (2.24 - 9.13)**	**3.94 (1.81 - 8.58)**
Bilirubin (increasing mg/dL)	1.15 (0.94 - 1.42)	
INR (increasing unit)	1.17 (0.36 - 3.81)	
Genotype (3 vs others)	1.68 (0.75 - 3.79)	**5.05 (1.75 - 14.57)**
Diabetes	0.95 (0.44 - 2.06)	
Anti-HBc+	**2.07 (1.12 - 3.84)**	**1.99 (1.01 - 3.95)**
HBsAg+	Not estimable**	
Previous Interferon	0.94 (0.50 - 1.79)	

Variables associated with decompensating event

Baseline factors	Crude HR (95% CI)	Adjusted HR (95% CI)
HIV infection	0.90 (0.32 - 2.49)	0.55 (0.07 - 4.32)
Age (increasing years)	**1.03 (1.00 - 1.05)**	**1.03 (1.00 - 1.07)**
Sex (ref. female)	1.58 (0.91 - 2.77)	**2.13 (1.06 - 4.26)**
BMI: overweight/obese (ref. under-normalweight)	0.93 (0.71 - 1.20)	
Current alcohol use (ref. never) Past alcohol use (ref. never)	1.36 (0.56 - 3.29) **2.17 (1.24 - 3.82)**	1.84 (0.97 - 3.50)
ALT (increasing IU/L)	1.00 (0.99 - 1.00)	
AST (increasing IU/L)	1.00 (0.99 - 1.01)	
Platelets (ref. >100,000/µL)	**1.95 (1.16 - 3.29)**	1.73 (0.93 - 3.20)
Albumin (decreasing g/dL)	**4.66 (2.54 - 8.56)**	**3.75 (1.89 - 7.46)**
Bilirubin (increasing mg/dL)	0.99 (0.69 - 1.42)	
INR (increasing unit)	**2.11 (1.27 - 3.50)**	
Genotype (3 vs others)	1.26 (0.57 - 2.79)	
Diabetes	1.57 (0.88 - 2.81)	
Anti-HBc+	0.47 (0.22 - 1.00)	
HBsAg+	1.03 (0.14 - 7.48)	
Previous Interferon	0.74 (0.41 - 1.32)	
HCC	1.85 (0.67 - 5.13)	

HIV coinfection was not associated with a higher probability of developing liver complications in cirrhotic patients, after viral eradication

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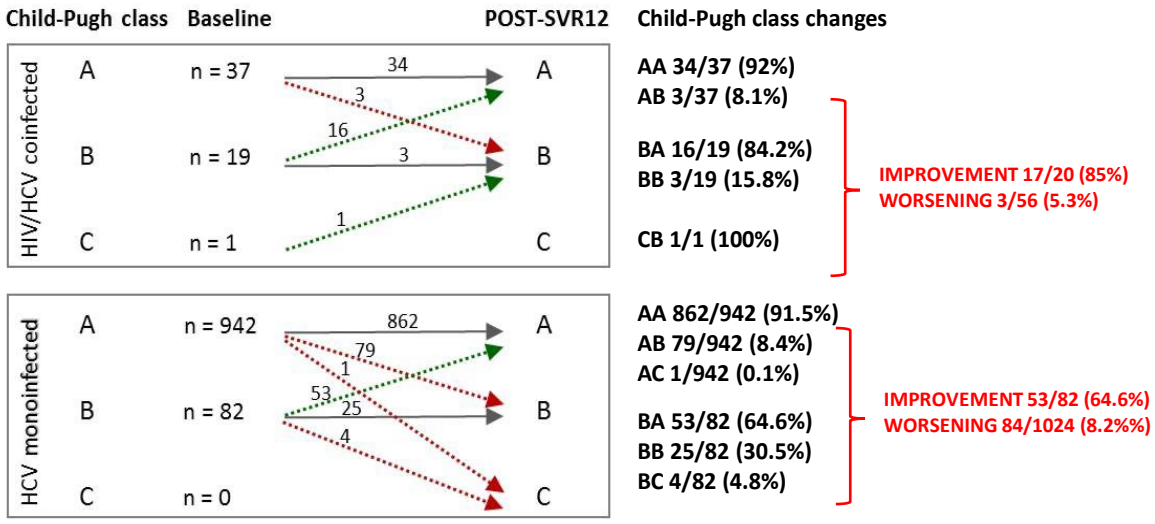
Baseline characteristics		HCV/HIV co-infected (N=108*) N.	%	HCV mono-infected (N=1242*) N.	%	p**
Previous decompensations	Yes	15	13.9	133	10.7	0.31
	No	93	86.1	1109	89.3	
Child-Pugh Score	A-5	39	52.7	762	69.5	**< 0.001**
	A-6	14	18.9	242	22.1	
	B-7	12	16.2	58	5.3	
	B-8	8	10.8	28	2.6	
	B-9	0	0.0	6	0.6	
	C-10	1	1.4	0	0.0	

Baseline factors associated with a more advanced liver disease before treatment (C-P class B/C vs A)

Baseline factors	Adjusted O.R.	95% CI
Age (increasing years)	1.00	0.98 -1.02
Sex (ref. female)	1.07	0.69 - 1.67
Current/past alcohol use (ref. never)	0.87	0.56 - 1.37
HCV-genotype (3 vs others)	1.48	0.80 - 2.76
HBsAg+	2.27	0.57 - 8.99
HIV+	**3.73**	**2.00 - 6.98**

Changes in the severity of liver disease in terms of C-P class improvement or worsening following viral eradication



Child-Pugh class changes

AA 34/37 (92%)
AB 3/37 (8.1%)

BA 16/19 (84.2%)
BB 3/19 (15.8%)

CB 1/1 (100%)

IMPROVEMENT 17/20 (85%)
WORSENING 3/56 (5.3%)

AA 862/942 (91.5%)
AB 79/942 (8.4%)
AC 1/942 (0.1%)

BA 53/82 (64.6%)
BB 25/82 (30.5%)
BC 4/82 (4.8%)

IMPROVEMENT 53/82 (64.6%)
WORSENING 84/1024 (8.2%%)

Variables associated with Child-Pugh class worsening following viral eradication

Baseline factors	Crude HR	95% CI	Adjusted HR	95% CI
HIV infection	0.68	0.21 - 2.15	0.51	0.15 - 1.73
Age (increasing years)	1.00	0.98 - 1.02	1.00	0.98 - 1.02
Sex (ref. female)	**1.77**	**1.12 - 2.81**	**2.00**	**1.18 - 3.36**
BMI: overweight/obese (ref. under-normalweight)	0.88	0.58 - 1.34	0.79	0.51 - 1.22
Current/past alcohol use (ref. never)	0.99	0.63 - 1.55	0.76	0.47 - 1.24
ALT (increasing IU/L)	1.00	0.99 - 1.00	1.00	0.99 - 1.01
AST (increasing IU/L)	1.00	0.99 - 1.00	0.99	0.98 - 1.00
Platelets (ref. >100,000/µL)	**2.01**	**1.31 - 3.08**	**1.75**	**1.08 - 2.85**
Albumin (decreasing g/dL)	1.57	0.99 - 2.43	1.35	0.82 - 2.23
Bilirubin (increasing mg/dL)	0.98	0.87 - 1.12	0.84	0.60 - 1.18
INR (increasing unit)	**2.15**	**1.45 - 3.19**	**2.41**	**1.51 - 3.84**
HCV-genotype (3 vs others)	1.51	0.80 - 2.84	1.54	0.75 - 3.17
Diabetes	1.14	0.69 - 1.89	0.93	0.55 - 1.57
Anti-HBc+	1.02	0.63 - 1.65	1.05	0.63 - 1.76
Previous Interferon treatment	0.82	0.52 - 1.29	0.77	0.48 - 1.23
Esophageal varices	**1.85**	**1.20 - 2.85**	1.47	0.89 - 2.42
HCC	**2.32**	**1.20 - 4.49**	1.88	0.87 - 4.08
Previous decompensating event	**1.97**	**1.17 - 3.31**	1.12	0.60 - 2.11

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Conclusion

- After successful DAA treatment, patients with advanced liver disease and HIV coinfection have a similar probability of developing liver complications as HCV monoinfected patients.

- “Curing” HCV is not the ultimate goal in patients with severe liver disease in both coinfected and monoinfected patients. Once a certain severity of liver damage had reached during viral replication liver disease could progress regardless of viral eradication in coinfected and monoinfected patients.

Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

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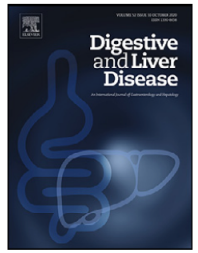

Liver, Pancreas and Biliary Tract

Clinical features and comorbidity pattern of HCV infected migrants compared to native patients in care in Italy: A real-life evaluation of the PITER cohort

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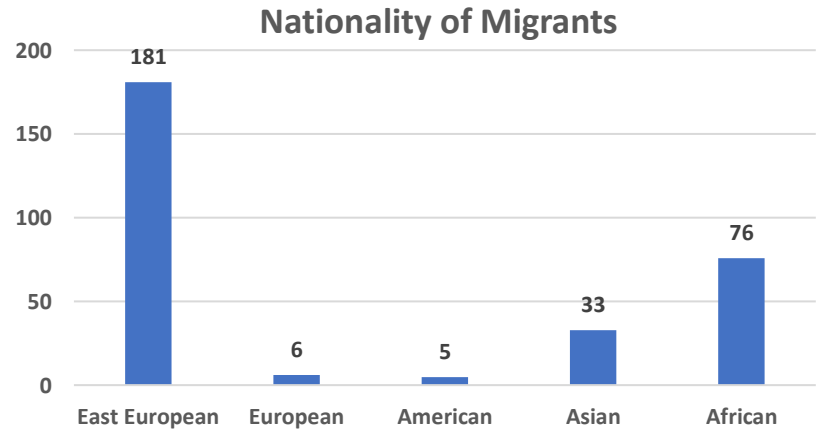
AIM

We aimed to evaluate demographic, virological and clinical data of HCV-infected migrants in care in Italy as compared to native Italians. In particular, we aimed to underline the pattern of comorbidities and other factors for liver disease progression that should be focused in the clinical practice after HCV eradication.

Migrants were defined as persons with country of birth and nationality different from Italy, whereas natives include person born in Italy and with Italian nationality.



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Migrant and Native patients baseline characteristics

Characteristics		Migrants (N=301*) Median	Range	Natives (N=10368*) Median	Range	p**	Adjusted*** O.R. (95% C.I.)
Age (years)		47	18 - 78	62	18 - 95	**< 0.001**	**0.92 (0.91 - 0.93)**
		N.	%	N.	%		
Sex	Male (Ref.)	131	43.5	5670	54.7	**< 0.001**	
	Female	170	56.5	4698	45.3		**2.49 (1.73 - 3.56)**
BMI	Normal (Ref.)	125	41.5	5078	49.0	**< 0.05**	
	Underweight	8	2.7	188	1.8		1.03 (0.40 - 2.66)
	Overweight-Obese	168	55.8	5101	49.2		**2.26 (1.58 - 3.24)**
Genotype	≠ 4 (Ref.)	229	79.5	9081	94.0	**< 0.001**	
	4	59	20.5	578	6.0		**2.51 (1.60 - 3.93)**
HBsAg+	No (Ref.)	229	96.2	7967	98.6	**< 0.05**	
	Yes	9	3.8	113	1.4		**2.67 (1.22 - 7.24)**
HIV+	No (Ref.)	183	94.8	5110	90.8	> 0.05	
	Yes	10	5.2	517	9.2		**0.29 (0.11 - 0.71)**
Alcohol use	Never (Ref.)	203	68.4	6562	64.4	> 0.05	
	Current	48	16.2	1661	16.3		0.84 (0.53 - 1.33)
	Past	46	15.5	1969	19.3		0.70 (0.43 - 1.15)
Previous Interferon	No (Ref.)	242	80.4	7593	73.2	**< 0.05**	
	Yes	59	19.6	2775	26.8		0.82 (0.55 - 1.24)
Liver Stiffness value	≤ 14 KPa (Ref.)	220	73.1	6344	61.2	**< 0.001**	
	> 14 KPa§	81	26.9	4024	38.8		1.14 (0.77 - 1.71)

No significant differences among migrants and native patients were observed for baseline ALT, AST, platelet count, serum albumin, bilirubin, creatinine, and INR values (p>0.05).

Genotype 1b was prevalent in both groups (53.5% and 48.9%, in migrants and natives respectively, p>0.05). Genotype 1a and 2 were more frequently observed in native compared to migrant patients (12.1% vs. 6.6% and 19.1% vs. 5.2%, respectively) whereas genotype 4 was more frequent in migrants compared to natives (20.5%, vs. 6.0%, respectively) (p<0.001).

A similar C-P class distribution (C-P class A: 87% vs 82.2%; C-P class B/C: 13% vs. 17.8% in migrants and natives, respectively, p>0.05) and a similar prevalence of decompensated cirrhosis (9.9% in migrants and 17.4% in natives, p>0.05), were observed in both groups.

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Similar rates of SVR12 were observed in migrants (98%) and natives (96%) patients (p>0.05).

Comorbidities distribution in migrant and native patients

Comorbidities		Migrants ($N=301$*)		Natives ($N=10{,}368$*)		p*
		N.	%	N.	%	
Autoimmune	No	295	98.0	9909	95.6	< 0.05
	Yes	6	2.0	459	4.4	
Cardiovascular	No	256	85.0	6436	62.1	< 0.001
	Yes	45	15.0	3932	37.9	
Cerebrovascular	No	301	100.0	10,306	99.4	> 0.05
	Yes	0	0.0	62	0.6	
Dermatologic	No	301	100.0	10,319	99.5	> 0.05
	Yes	0	0.0	49	0.5	
Type 2 Diabetes	No	275	91.4	8896	85.8	< 0.05
	Yes	26	8.6	1472	14.2	
Dyslipidemia	No	293	97.3	9822	94.7	< 0.05
	Yes	8	2.7	546	5.3	
Endocrine	No	296	98.3	9866	95.2	< 0.05
	yes	5	1.7	502	4.8	
hematological	no	295	98.0	9840	94.9	< 0.05
	Yes	6	2.0	528	5.1	
Neurological	No	298	99.0	10,018	96.6	< 0.05
	Yes	3	1.0	350	3.4	
Psychiatric	No	294	97.7	9519	91.8	< 0.001
	Yes	7	2.3	849	8.2	
Renal	No	294	97.7	10,031	96.7	> 0.05
	Yes	7	2.3	337	3.3	
Respiratory	No	299	99.3	10,268	99.0	> 0.05
	Yes	2	0.7	100	1.0	
Tumors	No	294	97.7	9660	93.2	< 0.001
	Yes	7	2.3	708	6.8	
Others	No	259	86.0	8861	85.5	> 0.05
	Yes	42	14.0	1507	14.5	

* p value Chi-square test.

Cofactors for liver disease progression in succesfully DAA treated migrant and native patients

	Migrants ($N=128$)		Natives ($N=4896$)		p*
	N.	%	N.	%	
HBsAg+	4	3.1	57	1.2	< 0.05
HIV+	6	4.7	290	5.9	> 0.05
Current alcohol use	19	14.8	740	15.1	> 0.05
Metabolic syndrome	24	18.8	1570	32.1	< 0.05
One or more cofactors	50	39.1	2304	47.1	> 0.05

* p value Chi-square test.

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Conclusion

- Compared to natives, HCV-infected migrants in care have different demographics, HCV genotypes, viral coinfections and comorbidities and similar disease severity, SVR and cofactors for disease progression after HCV eradication.

- It is important to properly address different comorbidities and maintain the clinical assessment in Italian and migrants with comorbidities and risk factors for liver disease progression after HCV eradication.

HEPATOLOGY

AASLD
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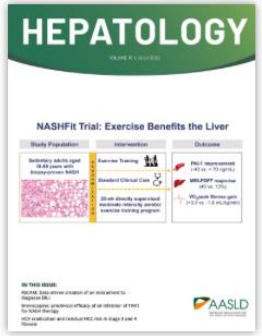

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A prospective study of direct-acting antiviral effectiveness and relapse risk in HCV cryoglobulinemic vasculitis by the Italian PITER cohort

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 ... See fewer authors

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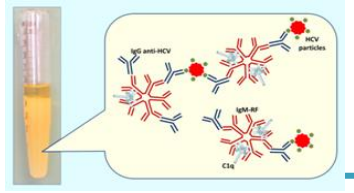
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.



CV Symptoms at enrollment

- PURPURA
- ASTHENIA
- ARTHRALGIA

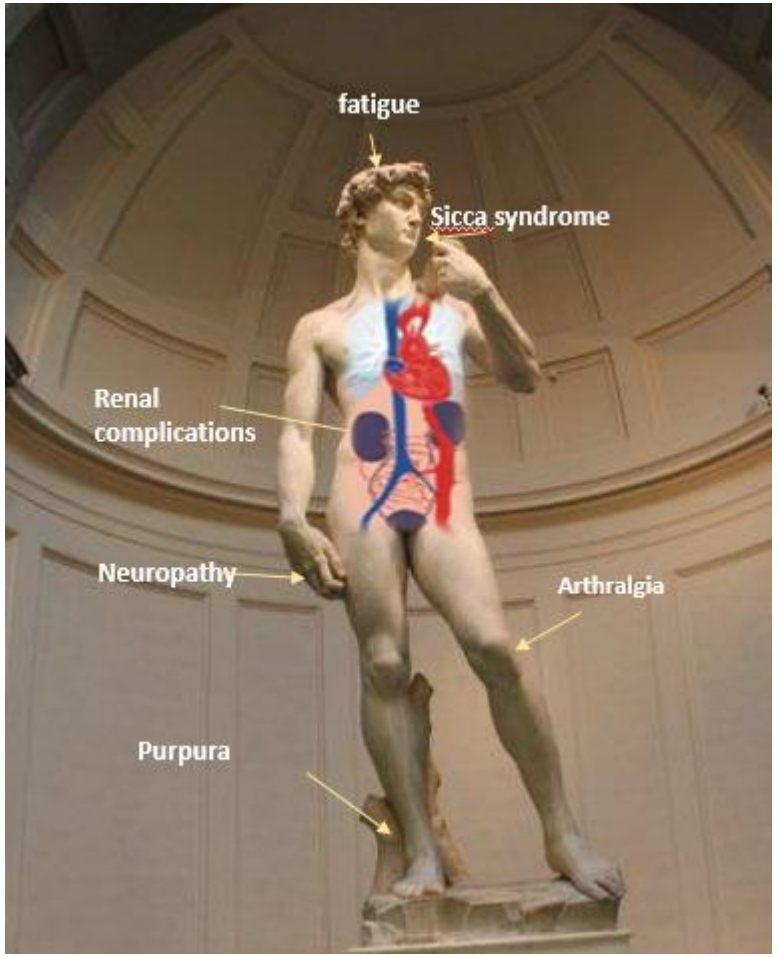
- NEUROPATHY
- SICCA SYNDROME. (xerostomia/xerophthalmia)

In 69% to 95% of patients

- RENAL INVOLVEMENT

(from proteinuria and hematuria to a frank reduction in GFR)

In 12.2% patients



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Conclusioni

- I risultati ottenuti indicano che dopo l'eradicazione virale, la persistenza o la ricorrenza di alcuni o della maggior parte dei sintomi pre-trattamento non è insolita.

- L'analisi prospettica dei pazienti crioglobulinemici arruolati consecutivamente nella coorte PITER e trattati con DAA, ha confermato che **dopo la SVR la maggior parte dei pazienti CV raggiunge una risposta clinica che aumenta nel tempo.**

- Tuttavia la **risposta clinica fluttua frequentemente**. Il pattern della manifestazione clinica può cambiare e riapparire, in modo persistente o transitorio, suggerendo un'attenta valutazione del paziente con CV anche dopo l'eradicazione virale.

- L'accurata valutazione degli indici prognostici, sia clinici che di laboratorio, emersi dal presente studio (possibilmente in combinazione con i marcatori della persistenza dell'espansione dei linfociti B clonali) aiuterà a prevedere diverse evoluzioni cliniche.

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

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Profiling the risk of hepatocellular carcinoma after long-term HCV eradication in patients with liver cirrhosis in the PITER cohort

Loreta A. Kondili[a,b,#], Maria Giovanna Quaranta[a], Luisa Cavalletto[c], Vincenza Calvaruso[d], Luigina Ferrigno[a], Roberta D'Ambrosio[e], Ilaria Simonelli[f], Giuseppina Brancaccio[g], Giovanni Raimondo[h], Maurizia R. Brunetto[i], Anna Linda Zignego[j], Carmine Coppola[k], Andrea Iannone[l], Elisa Biliotti[m], Gabriella Verucchi[n], Marco Massari[o], Anna Licata[p], Francesco Barbaro[q], Marcello Persico[r], Francesco Paolo Russo[s], Filomena Morisco[t], Maurizio Pompili[u], Mauro Viganò[v], Massimo Puoti[w,x], Teresa Santantonio[y], Erica Villa[z], Antonio Craxì[d], Liliana Chemello[c,##], on behalf of PITER Collaborating Investigators*

Dig Liver Dis . 2023 Feb 10;S1590-8658(23)00164-0. doi: 10.1016/j.dld.2023.01.153

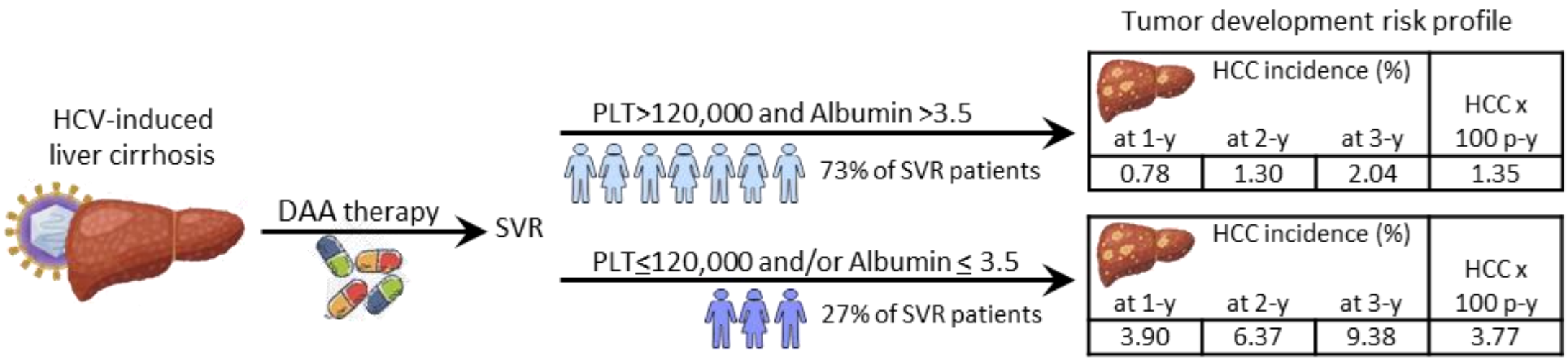

HCV-induced
liver cirrhosis
DAA therapy
SVR
PLT>120,000 and Albumin >3.5
73% of SVR patients
PLT≤120,000 and/or Albumin ≤ 3.5
27% of SVR patients
Tumor development risk profile
HCC incidence (%)
at 1-y
at 2-y
at 3-y
HCC x
100 p-y
0.78
1.30
2.04
1.35
HCC incidence (%)
at 1-y
at 2-y
at 3-y
HCC x
100 p-y
3.90
6.37
9.38
3.77

Table 1 - Baseline characteristics of DAA successfully treated patients by HCC occurrence.

		No HCC (N=1945)		HCC occurrence (N=119)			TOTAL (N=2064)	
Epidemiological features		Median (IQR)		Median (IQR)		p**	Median (IQR)	
Age (years)		64 (54 - 72)		68 (62 - 72)		**<0.001**	64 (55 - 72)	
		N.	%	N.	%	p***	N.	%
Gender	Male	1099	56.5	73	61.3	0.301	1172	56.8
	Female	846	43.5	46	38.7		892	43.2
BMI*	Underweight-Normal	860	44.3	57	47.9	0.625	917	44.5
	Overweight	783	40.3	47	39.5		830	40.3
	Obese	300	15.4	15	12.6		315	15.3
Alcohol use*	Never	1299	68.8	74	63.3	0.373	1373	68.4
	Current	205	10.9	13	11.1		218	10.9
	Past	385	20.4	30	25.6		415	20.7
HCV- genotype	1a	248	12.8	7	5.9	0.207	255	12.4
	1b	1107	56.9	72	60.5		1179	57.1
	2	289	14.9	17	14.3		306	14.8
	3	181	9.3	15	12.6		196	9.5
	Other	120	6.2	8	6.7		128	6.2
HBV Infection	Anti-HBc+/HBsAg+	22	1.1	0	0.0	0.386	22	1.1
	Anti-HBc+/HBsAg-	383	19.7	27	22.7		410	19.9
Potential metabolic syndrome		253	13.0	15	12.6	0.899	268	13.0
Diabetes		415	21.3	35	29.4	**0.038**	450	21.8
Previous Interferon use		905	46.5	64	53.8	0.124	969	46.9
Clinical features		N.	%	N.	%	p***	N.	%
Platelets count (μL)*	≤ 120,000/μL	979	51.9	82	70.7	**<0.001**	1061	53.0
	> 120,000/μL	908	48.1	34	29.3		942	47.0
Albumin level (g/dL)*	≤ 3.5	400	22.9	54	47.8	**<0.001**	454	24.5
	> 3.5	1343	77.1	59	52.2		1402	75.5
Liver Stiffness	≥ 20	714	46.8	54	60.7	**0.011**	768	47.5
Measurement (kPa)*	< 20	813	53.2	35	39.3		848	52.5
FIB-4*	≤ 3.25	629	33.6	22	19.1	**0.001**	651	32.8
	> 3.25	1243	66.4	93	80.9		1336	67.2
Child-Pugh Class	A	1663	85.5	93	78.2	**0.029**	1756	85.1
	B	282	14.5	26	21.8		308	14.9
Past decompensation§		204	10.5	21	17.6	**0.015**	225	10.9
Treatment regimen		N.	%	N.	%	p***	N.	%
Ribavirin use		1119	57.5	76	63.9	0.174	1195	57.9
SOF-based treatment		1499	77.1	102	85.7	**0.028**	1601	77.6

* Inconsistencies are due to missing values
** p value Mann–Whitney rank-sum test
*** p value Chi-square test
§ All patients did not have sign of liver decompensation at treatment start

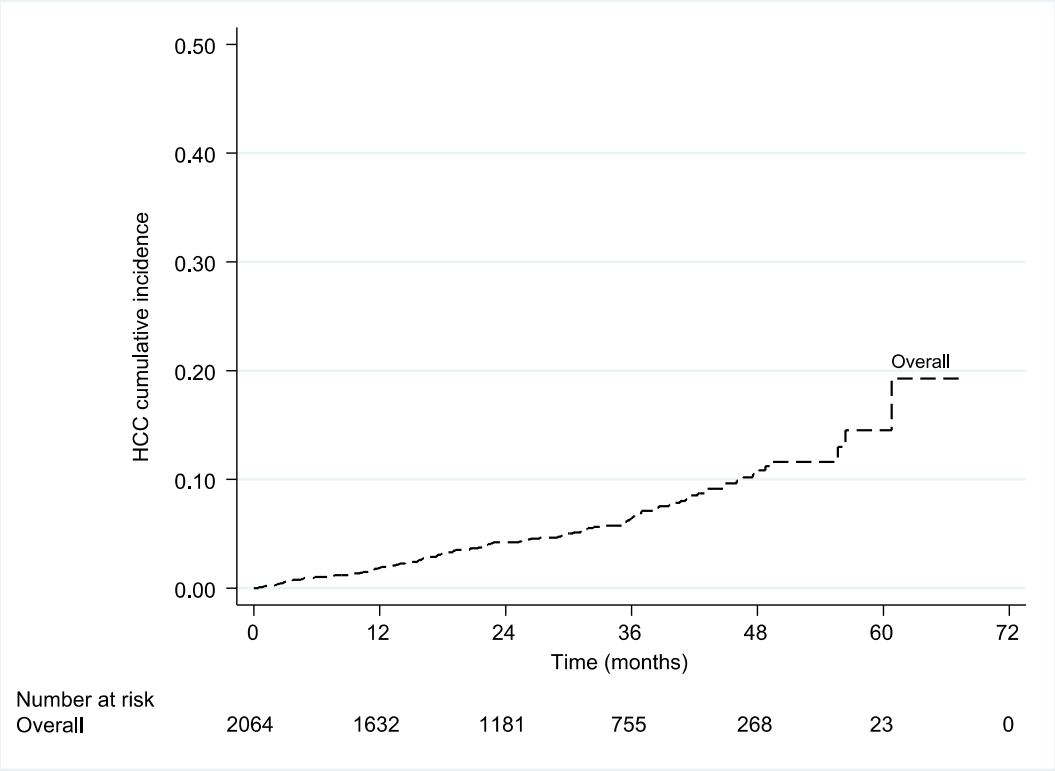
Table 2 - Variables associated with HCC occurrence in DAA successfully treated patients. Univariate and multivariate analysis.

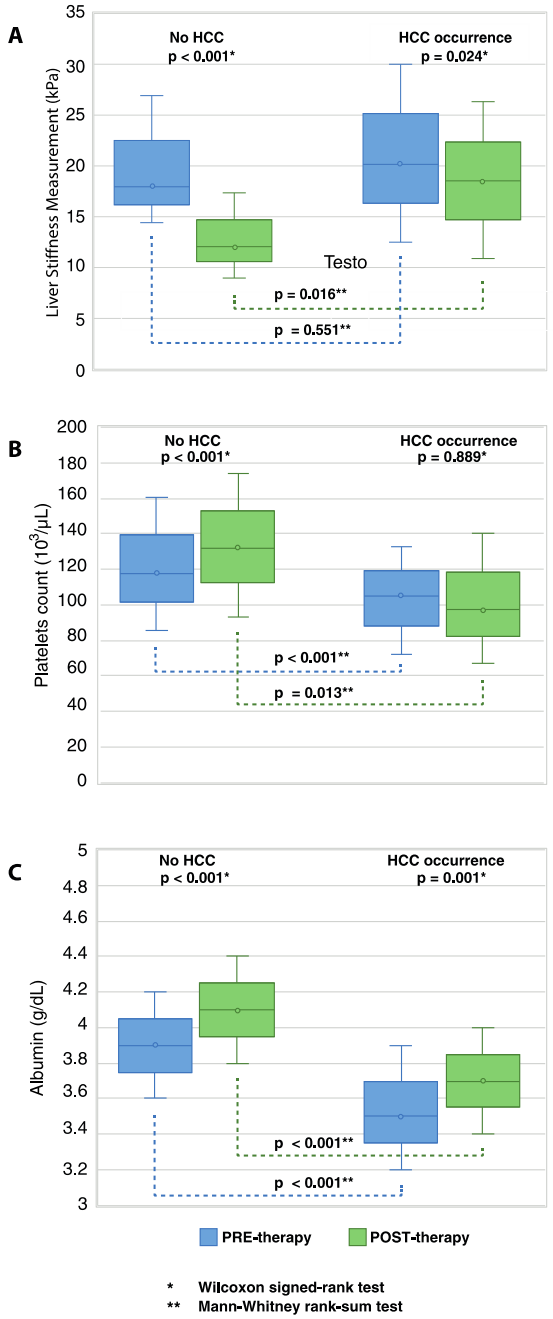
Pre-treatment factors	Crude HR	95% CI	p value	Adjusted HR*	95% CI	p value
Age (increasing years)	**1.04**	**1.02 - 1.06**	**<0.001**	**1.06**	**1.04 - 1.09**	**<0.001**
Gender (ref. female)	1.32	0.91 - 1.91	0.139	1.39	0.89 - 2.17	0.143
BMI: overweight (ref. under-normalweight)	0.91	0.62 - 1.33	0.615			
obese (ref. under-normalweight)	0.86	0.49 - 1.51	0.596			
Alcohol use: current (ref. never)	1.38	0.76 - 2.48	0.290			
past (ref. never)	1.36	0.89 - 2.08	0.157			
HCV-genotype (3 vs others)	1.49	0.87 - 2.57	0.146	**4.27**	**2.22 - 8.23**	**<0.001**
Anti-HBc$^+$	1.14	0.74 - 1.76	0.542	1.58	0.98 - 2.55	0.058
Previous Interferon treatment	1.11	0.78 - 1.60	0.563			
Platelets count (ref. >120,000/μL)	**1.95**	**1.30 - 2.90**	**0.001**	**1.67**	**1.05 - 2.65**	**0.029**
Albumin level (ref. > 3.5 g/dL)	**3.08**	**2.13 - 4.46**	**<0.001**	**2.51**	**1.62 - 3.88**	**<0.001**
LSM (ref. < 20 kPa)	1.50	0.98 - 2.30	0.063			
Past decompensation	**1.74**	**1.09 - 2.80**	**0.021**			
Diabetes	**1.56**	**1.05 - 2.31**	**0.027**	**1.75**	**1.10 - 2.76**	**0.017**
Ribavirin use	0.82	0.56 - 1.20	0.300			
SOF-based treatment	**1.72**	**1.03 - 2.88**	**0.038**			

* Cox forward stepwise selection. Gender variable was forced to be included in the model.

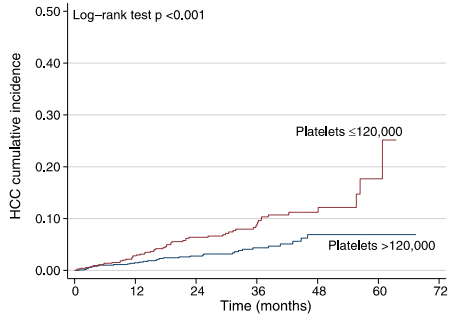
Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; DAA, Direct Acting Antiviral; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; HR, Hazard Ratio; LSM, Liver Stiffness Measurement; SOF, Sofosbuvir.

A


0.50
0.40
0.30
0.20
0.10
0.00
HCC cumulative incidence
Overall
0
12
24
36
48
60
72
Time (months)
Number at risk
Overall
2064
1632
1181
755
268
23
0

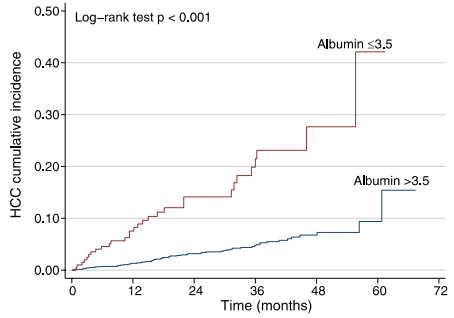

A
No HCC
p < 0.001*
HCC occurrence
p = 0.024*
Liver Stiffness Measurement (kPa)
35
30
25
20
15
10
5
0
Testo
p = 0.016**
p = 0.551**
B
No HCC
p < 0.001*
HCC occurrence
p = 0.889*
Platelets count (10^3/µL)
200
180
160
140
120
100
80
60
40
20
0
p < 0.001**
p = 0.013**
C
No HCC
p < 0.001*
HCC occurrence
p = 0.001*
Albumin (g/dL)
5
4.8
4.6
4.4
4.2
4
3.8
3.6
3.4
3.2
3
p < 0.001**
p < 0.001**
PRE-therapy
POST-therapy
* Wilcoxon signed-rank test
** Mann-Whitney rank-sum test

A



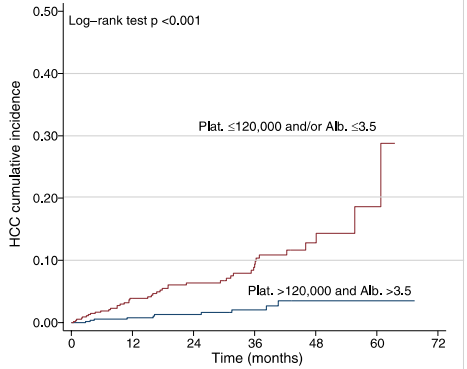
Number at risk							
Platelets >120,000	997	799	544	333	121	5	0
Platelets ≤120,000	736	591	428	272	96	15	0

B



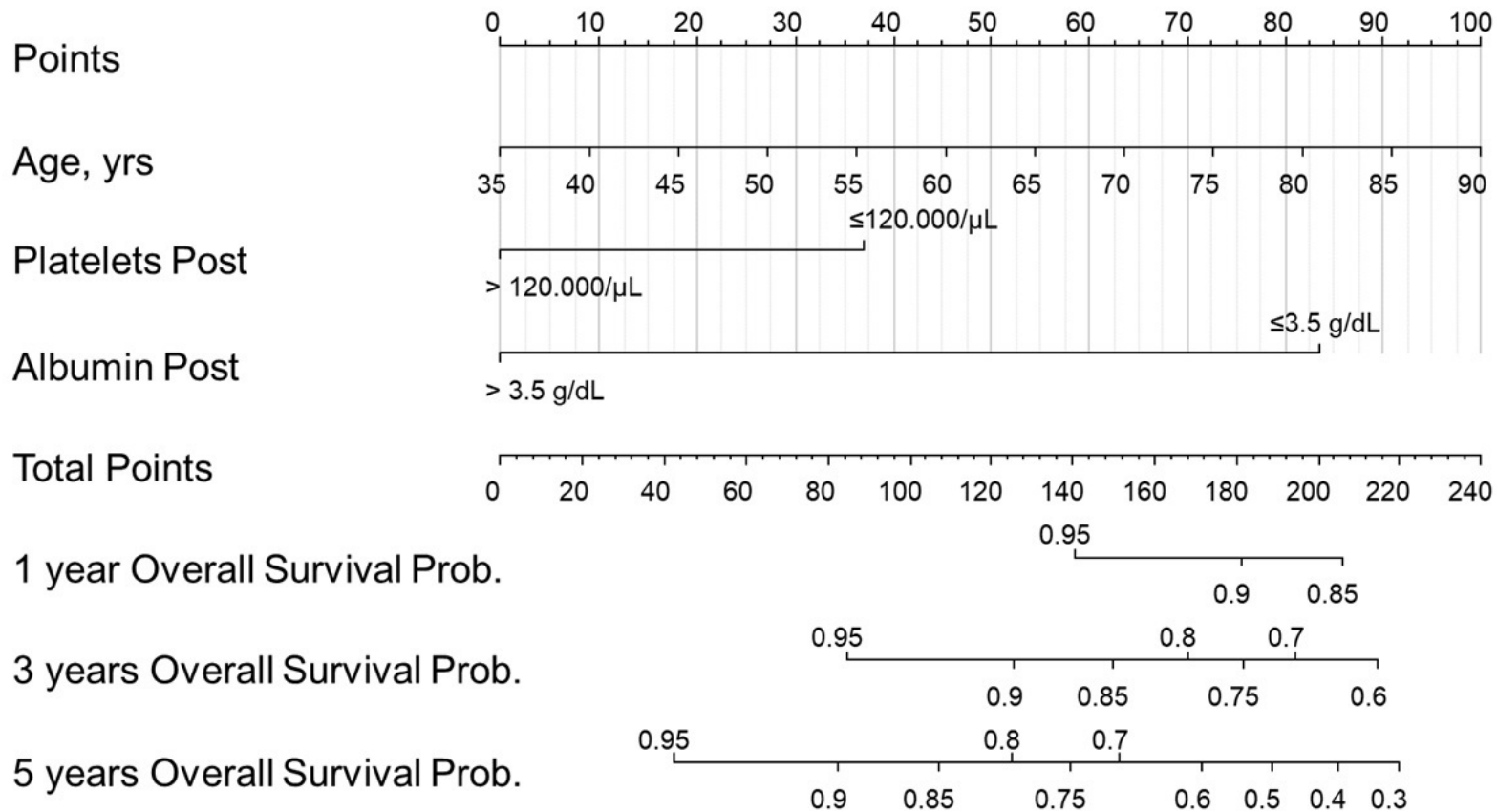
Number at risk							
Albumin >3.5	1389	1165	850	528	187	18	0
Albumin ≤3.5	200	140	78	49	13	1	0

C



Number at risk							
Plat. >120,000 and Alb. >3.5	548	420	310	177	48	2	0
Plat. ≤120,000 and/or Alb. ≤3.5	542	396	299	186	57	8	0

Variables	Crude HR	95% CI	p value	Adjusted HR	95% CI	p value
Age (increasing years)	1.04	1.02 - 1.06	<0.001	1.03	1.00 - 1.06	0.021
Platelets (ref. >120,000/µL)	2.48	1.41 - 4.35	0.002	1.92	1.06 - 3.45	0.030
Albumin (ref. > 3.5 g/dL)	4.94	2.83 - 8.63	<0.001	4.38	2.48 - 7.75	<0.001



Results

- After the end-of-therapy (median FU: 28.47 months), among 2064 SVR patients, 119 (**5.8%**) developed *de-novo* HCC.
- The HCC incidence was 1.90%, 4.21%, 6.47% at 12-, 24- and 36-months from end-of-therapy, respectively (incidence rate 2.45/100 person-years).
- Age, genotype 3, diabetes, platelets (PLT)≤120,000/µl and albumin ≤3.5g/dl were identified as pre-treatment HCC independent predictors.
- Adjusting for age, the post-treatment PLT≤120,000/µl and albumin≤3.5g/dl were independently associated with HCC occurrence.
- Two different risk profiles were identified by combining post-therapy evaluation of PLT ≤ or >120,000/µl and albumin ≤ or >3.5g/dl with an HCC incidence rate of 1.35 vs 3.77/100 p-y, respectively.

PITER

Piattaforma Italiana per lo studio
della Terapia delle Epatiti viRali.

PITER come strumento utile per i decisori politici

Strategie di Eliminazione dell'infezione da HCV ed evoluzione delle politiche sanitarie in Italia-Evidenze a Supporto da PITER

2015 2016 2017 2018 2019 2020 2021

Accesso Prioritizzato allaTerapia Antivirale

Accesso Universale alla Terapia Antivirale

Fondo dedicato farmaci Innovativi

Accesso Universale

Screening Attivo Approvato

Scadenza del Fondo Innovativo per i DAA

2017: Accesso universale è costo-efficace versus accesso prioritizato.

2019: Lo screening attivo è costo efficace versus il trattamento dei pazienti ad oggi *linkedto care*.

		2018	2019
Trattamenti Annuali		56,499	36,348
Anno in cui i Target OMS per l'eliminazione saranno raggiuti	Incidenza	2028	2037
	Mortalità	2023	2025
	Diagnosi	*	2037
	Tratamento	2029	2035
Anno di Eliminazione		**2029**	**>2038**
***On Track* per l'eliminazione**		**SI**	**No**

Investimento Continuo in Screening e Terapia anti- HCV elementi indispensabile ai fini dell'eliminazione HCV

Evidenze Economiche a supporto per l'allocazione fondi ad hoc per screening e trattamento

Eliminazione dell'infezione da HCV
PITER produce evidenze a supporto delle Politiche Sanitarie

HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 66, NO. 6, 2017

Modeling Cost-Effectiveness and Health Gains of a "Universal" Versus "Prioritized" Hepatitis C Virus Treatment Policy in a Real-Life Cohort

Loreta A. Kondili,[1] Federica Romano,[2] Francesca Romana Rolli,[2] Matteo Ruggeri,[2] Stefano Rosato,[1] Maurizia Rossana Brunetto,[3] Anna Linda Zignego,[4] Alessia Ciancio,[5] Alfredo Di Leo,[6] Giovanni Raimondo,[7] Carlo Ferrari,[8] Gloria Taliani,[9] Guglielmo Borgia,[10] Teresa Antonia Santantonio,[11] Pierluigi Blanc,[12] Giovanni Battista Gaeta,[13] Antonio Gasbarrini,[2] Luchino Chessa,[14] Elke Maria Erne,[15] Erica Villa,[16] Donatella Ieluzzi,[17] Francesco Paolo Russo,[15] Pietro Andreone,[18] Maria Vinci,[19] Carmine Coppola,[20] Liliana Chemello,[15] Salvatore Madonia,[21] Gabriella Verucchi,[18] Marcello Persico,[22] Massimo Zuin,[23] Massimo Puoti,[19] Alfredo Alberti,[15] Gerardo Nardone,[13] Marco Massari,[24] Giuseppe Montalto,[25] Giuseppe Foti,[26] Maria Grazia Rumi,[23] Maria Giovanna Quaranta,[1] Americo Cicchetti,[2] Antonio Craxì,[25] and Stefano Vella,[1] on behalf of the PITER Collaborating Group*

Liver INTERNATIONAL

ORIGINAL ARTICLE | Open Access

Optimization of hepatitis C virus screening strategies by birth cohort in Italy

Loreta A. Kondili, Ivane Gamkrelidze, Sarah Blach, Andrea Marcellusi, Massimo Galli, Salvatore Petta, Massimo Puoti, Stefano Vella, Homie Razavi, Antonio Craxi, Francesco S. Mennini, on behalf of the PITER collaborating group, ... See fewer authors

Liver INTERNATIONAL

ORIGINAL ARTICLE | Open Access

The impact of direct acting antivirals on hepatitis C virus disease burden and associated costs in four european countries

Francesco S. Mennini, Andrea Marcellusi, Sarah Robbins Scott, Simona Montilla, Antonio Craxi, Maria Buti , Liana Gheorghe, Stephen Ryder, Loreta A. Kondili

Springer Link

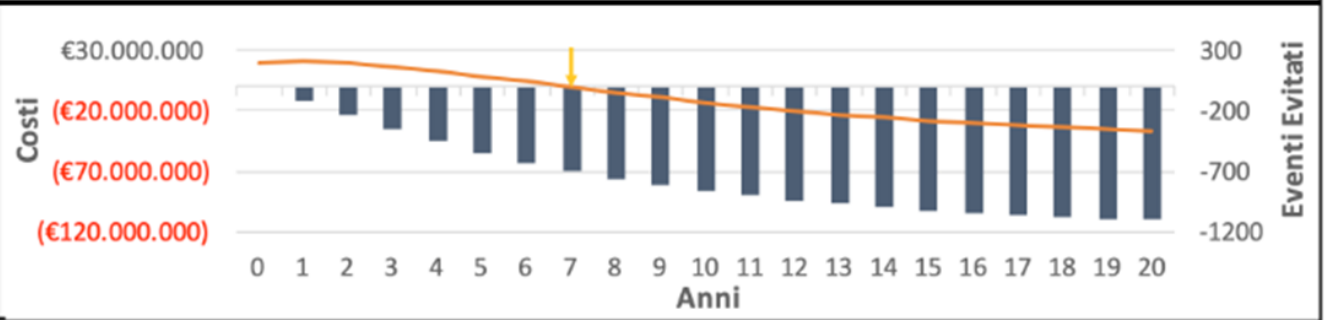
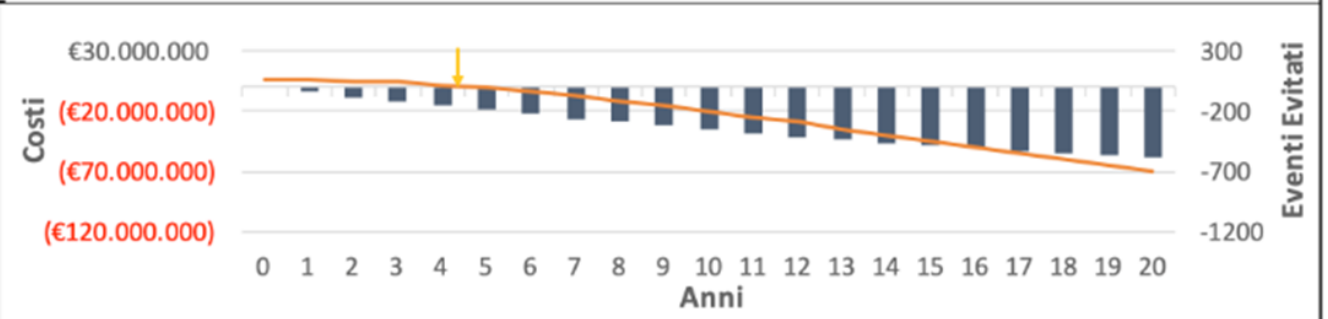
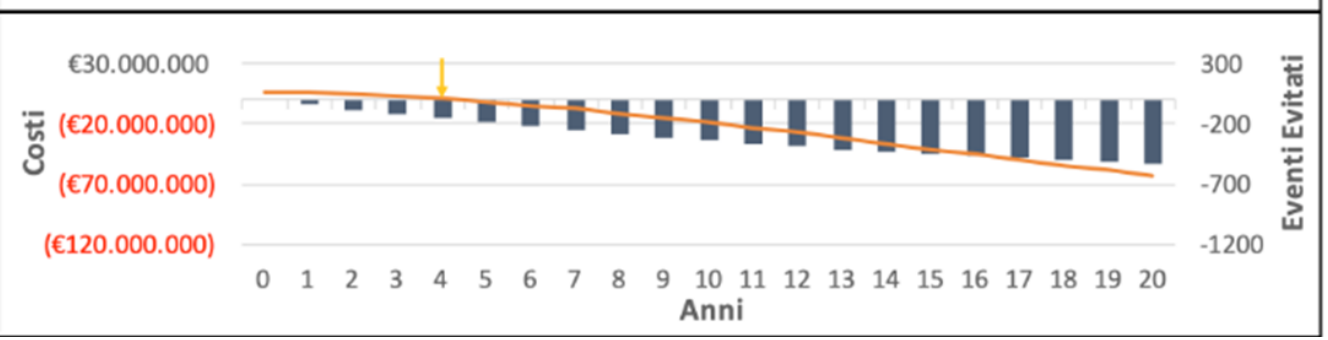
Original Research Article | Open Access | Published: 12 October 2021

Economic Consequences of Anti-HCV Treatment of Patients Diagnosed Through Screening in Italy: A Prospective Modelling Analysis

Andrea Marcellusi, Claudia Simonelli, Francesco S. Mennini, Loreta A. Kondili on behalf of PITER Collaborating Group available at http://www.progettopiter.it

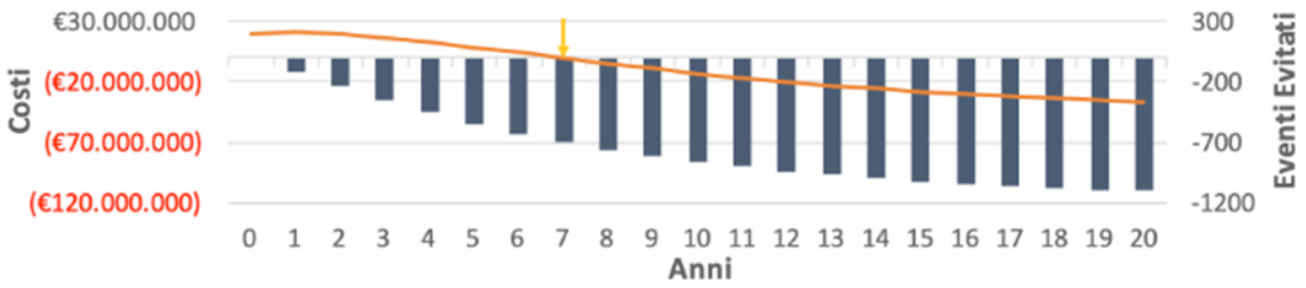
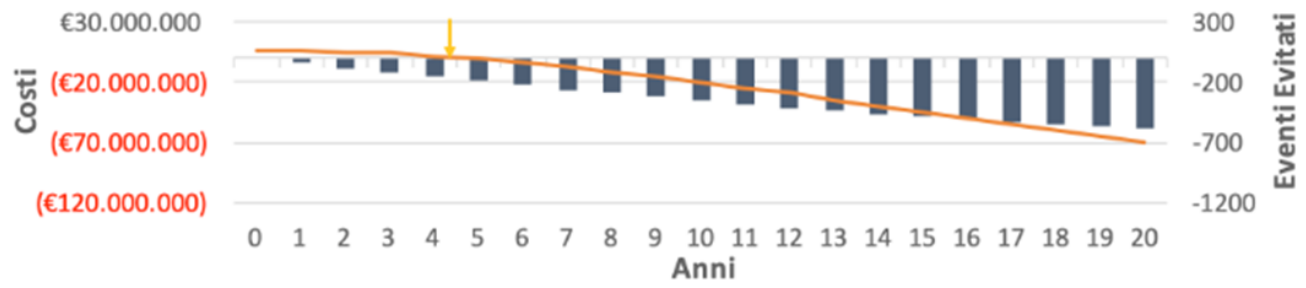
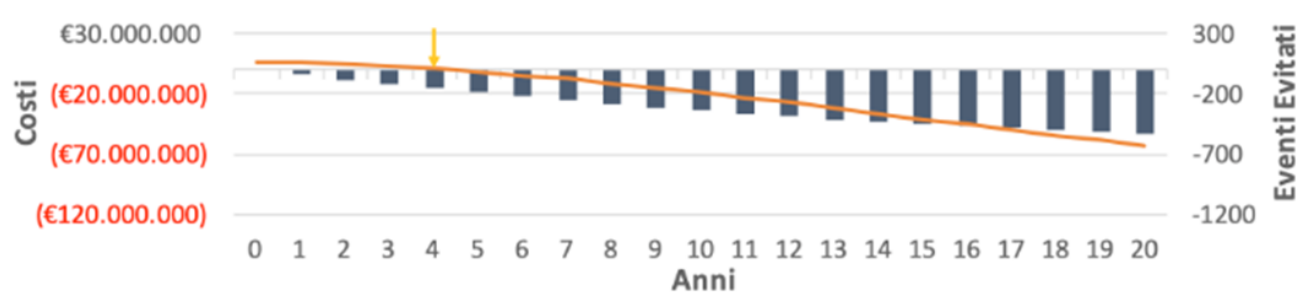
Applied Health Economics and Health Policy (2021) | Cite this article

RITORNO D'INVESTIMENTO PER LA TERAPIA ANTI-HCV IN ITALIA

Periodo di analisi	Ritorno investimento, anni	Eventi evitati dopo 20 anni	Costo evitato dopo 20 anni (€ milioni)	Eventi evitati / Differenza di costo evitato vs non trattamento
2015-2016 Prioritizzato	7,0	-1099	-€36.1	
2017-2019 Universale	4,8	-579	-€70.2	
Nuovi diagnosticati	4,4	-536	-€63.6	

Marcellusi, C Simonelli, F. Mennini L Kondili Applied Health Economics and Health Policy 2021 in press
Marcellusi, Mennini FS, Kondili L et al Liver International 2021.

RITORNO D'INVESTIMENTO PER LA TERAPIA ANTI-HCV IN ITALIA

Periodo di analisi	Ritorno investimento, anni	Eventi evitati dopo 20 anni	Costo evitato dopo 20 anni (€ milioni)	Eventi evitati / Differenza di costo evitato vs non trattamento
2015-2016 Prioritizzato	7,0	-1099	-€36.1	
2017-2019 Universale	4,8	-579	-€70.2	
Nuovi diagnosticati	4,4	-536	-€63.6	

Marcellusi, C Simonelli, F. Mennini L Kondili Applied Health Economics and Health Policy 2021 in press
Marcellusi, Mennini FS, Kondili L et al Liver International 2021.

Il Decreto Legge sullo screening gratuito dell'infezione attiva da HCV
Evidenze Scientifiche a supporto

Direct costs and health effects, by scenario, 2018–2031

Scenario		Cost (€Millions), 2018–2031	QALYs Gained, 2018–2031	ICER Relative to Status Quo (€/QALY)	ICER relative to previous least costly scenario (€/QALY)
Status quo		5,463	–	–	
GHSS Targets	**Graduated screening 1**	**5,974**	**144,000**	**3,552**	**3,552**
	Graduated screening 2	6,028	125,000	4,532	*
	Screening 1948–1977	6,081	142,000	4,349	*
	Screening 1958–1977	6,083	128,000	4,831	*
	Universal screening	6,441	145,000	6,758	562,855

- **Graduated Screening 1**: start screening in birth cohorts 1968–87 in year 2020 –identify young population at higher probability of HCV transmission risk
- expand screening for birth cohorts 1948–67 starting from 2023 – identify older population at risk for disease progression.

Art. 25-*bis*.
(Screening *nazionale gratuito per eliminazione del virus HCV)*

1. In via sperimentale, per il biennio 2020-2021, al fine di prevenire, eliminare ed eradicare il virus da epatite C (HCV) è garantito uno *screening* gratuito per i nati negli anni dal 1969 al 1989, per i soggetti che sono seguiti dai servizi pubblici per le tossicodipendenze (SerT), nonché per i soggetti detenuti in carcere.

Kondili LA, Gamkrelidze I, Blach S et al Liver international 2020
Mennini FS, Marcellusi A, Robbins et al Liver International 2021
Marcellusi A, Simonelli C, Mennini F Kondili LA Applied Health Economics and Health Policy 2021 *in press*

Lo screening e il linkage to care al fine dell'eliminazione di HCV in Italia

- L'investimento di 71,5 milioni riguarda solo la prima parte dello screening graduato raccomandato

- **Bisogna garantire fondi dedicati e l'efficienza del sistema per lo screening di tutta la coorte di nascita 1948-1988, come indicato in Italia ai fini dell'eliminazione di HCV .**
- Lo screening è solo il punto di partenza; all'efficienza degli screening deve corrispondere un rapido *linkage to care* e avviamento dei pazienti ai trattamenti.

Indispensabile

- Aumentare la sensibilizzazione la formazione e l'informazione dei medici e personale sanitario.
- Aumentare la sensibilizzazione e l'aderenza allo screening della popolazione generale e delle popolazioni chiave.
- Preparare e distribuire materiale informativo attraverso sistemi convenzionali riconosciuti (Patients decison aids).

Utile ed efficiente

- L'implementazione di strategie che abbinano lo screening e la vaccinazione di **SARS CoV-2 con lo screening per l'infezione da HCV.**

Kondili LA, Aghemo A, Andreoni A et al Digestive and Liver Disease 2021
Kondili LA, Craxi A, Aghemo A. Liver International 2021