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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

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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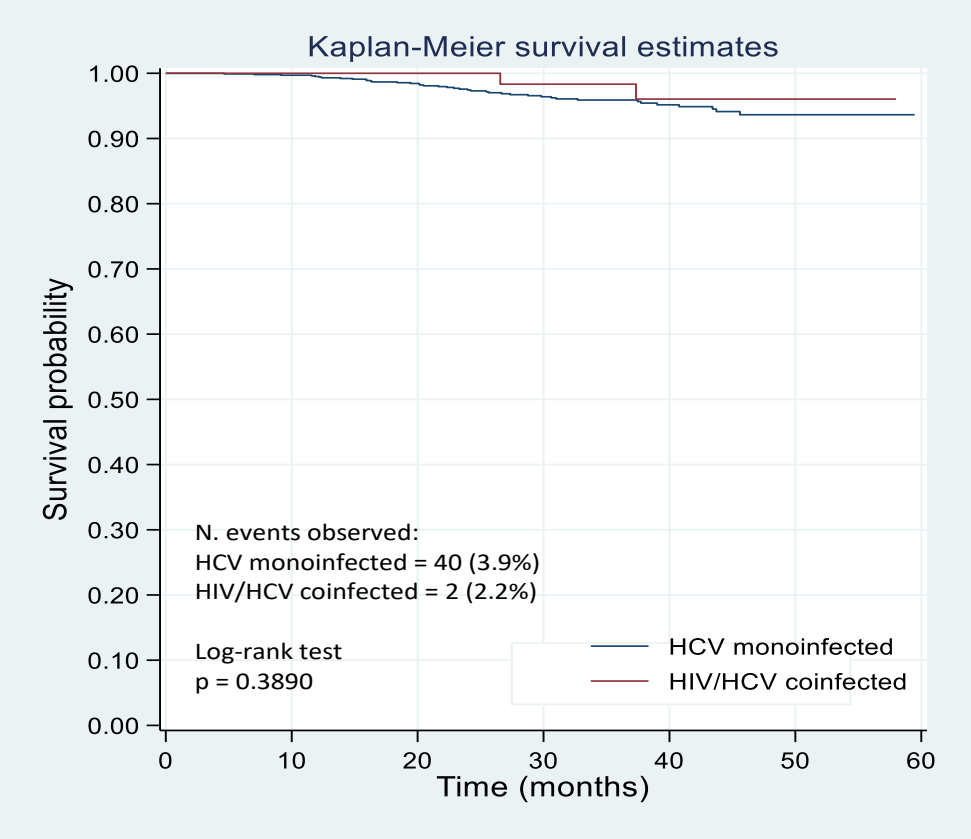
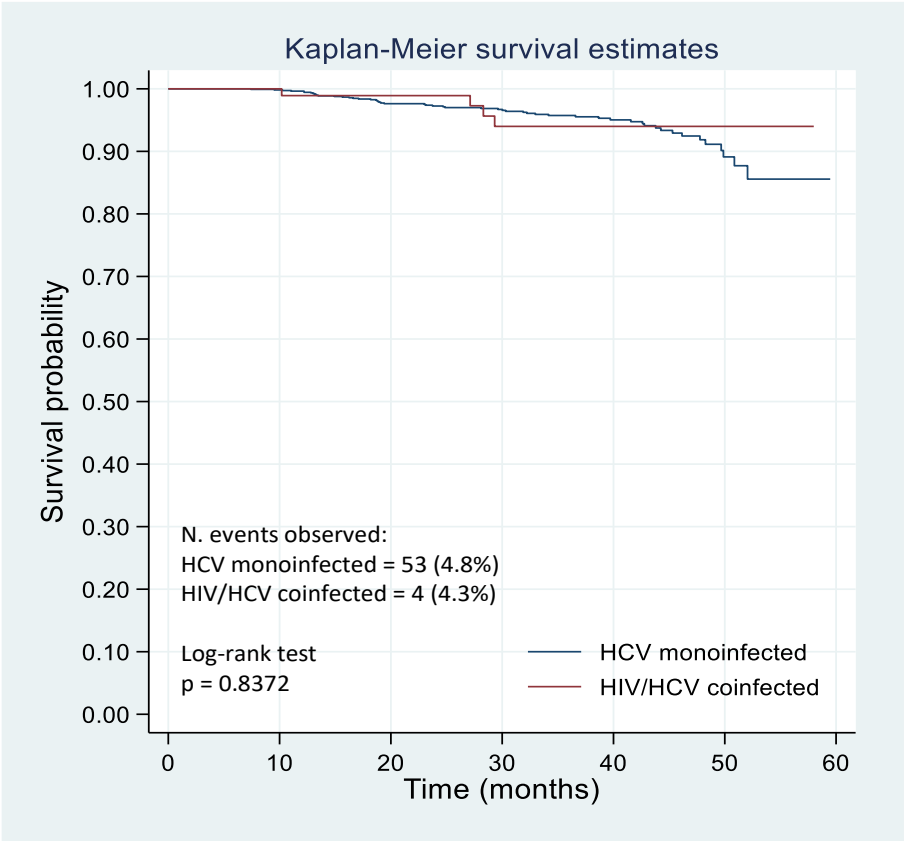
Liver related outcomes following viral eradication



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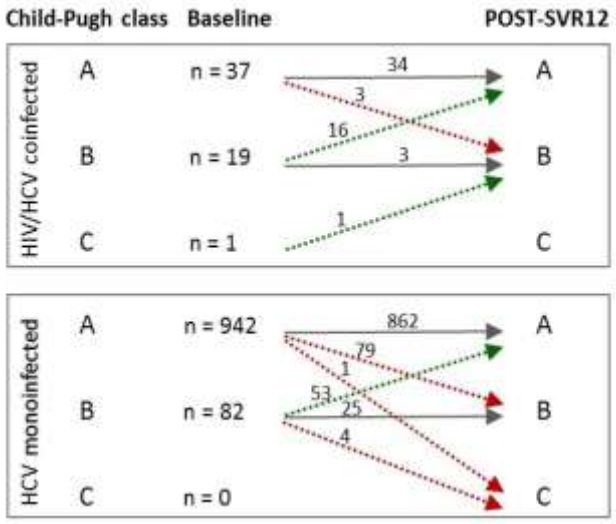
Baseline characteristics		HCV/HIV co-infected (N=108*) N.	%	HCV mono-infected (N=1242*) N.	%	p**
Previous decompensations	Yes	15	13.9	133	10.7	0.31
	No	93	86.1	1109	89.3	
Child-Pugh Score	A-5	39	52.7	762	69.5	**< 0.001**
	A-6	14	18.9	242	22.1	
	B-7	12	16.2	58	5.3	
	B-8	8	10.8	28	2.6	
	B-9	0	0.0	6	0.6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

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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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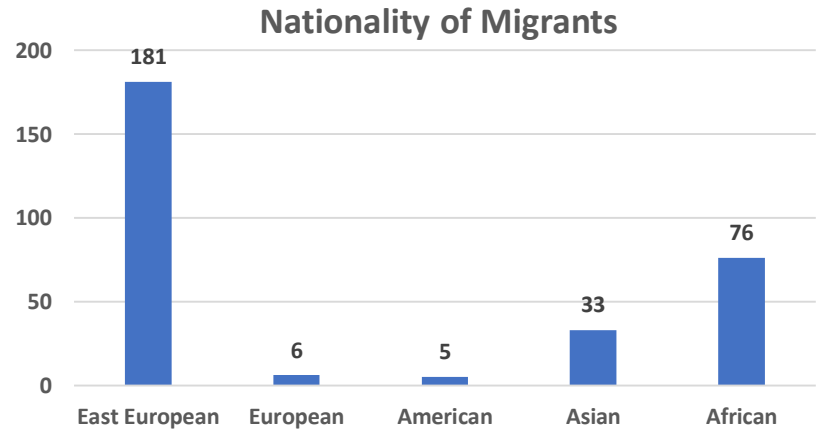
AIM

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.

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