The weight of pre-existing cofactors for liver disease progression in patients who successfully eradicated HCV virus infection: An interim analysis in the PITER cohort

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INTRODUCTION

Other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease, should be systematically investigated. EASL Clinical Practice Guidelines, suggest that HCV patients who achieve an SVR need to be maintained on follow-up in the presence of pre-existing cofactors for liver disease such as excessive alcohol drinking, obesity and/or type 2 diabetes. The contribution of comorbidities to the progression of liver disease must be evaluated and appropriate corrective measures implemented (Evidence base A1).

AIM

In the PITER (Italian platform for the Study of Viral Hepatitis Therapies) cohort we evaluated the real life management of patients following HCV eradication according to liver disease stage and presence of cofactors (CF) for liver disease progression.

METHOD

Patients: Only centers that have filled each electronic Case Report Form of enrolled patients in the PITER dbase up to November 2019 were included in the analysis. All consecutive patients enrolled by those clinical centers, who were treated and have an SVR post-treatment were included in the analysis. An available follow-up post SVR 12 for the outcome analysis was considered > 6 months.

The presence of Ultrasound fat and Hypertension/Cardiovascular disease as surrogate markers of NAFLD, or BMI>25, or Diabetes or Current Alcohol use were considered as CF for liver disease progression following viral eradication.

A decompensated event was considered in patients with liver cirrhosis who had before or after the SVR 12 at least one of the following events: ascitis, encefalopathy, hemorrhage from portal hypertension.

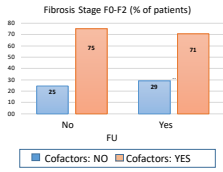
Chi square, Fisher exact or T student test were used for non parametric and continuous variables respectively. Cox Regression Analysis according to a stepwise selection was used to evaluate the predictive factors of the HCC and a decompensated event following the SVR12.

RESULTS

Patients' characteristics according to the fibrosis stage prior to antiviral treatment

Fibrosis stage	N patients	Mean Age (SD) (years)	Gender M/F (%)	Presence of CF for Disease progression	Available follow-up ≥12 months N Patients (%)	Mean (range follow-up) Months
F1-F2	1557	57 (13)	753/804 (48 /52)	1152 74%	464 (30) *	27 (19-36)
F3	473	61 (12)	259/214 (55/54)	396 84%	275 (58)*	32 (13-49)
F4/Cirrhosis	2008	63 (10)	1188/820 (59/41)	1712 85%	1089 (54)	33 (26-45)

**The remaining F0-F3 patients have no or less than 12 months follow-up following the SVR12 and lost to follow up for at least other 12 months following the last follow up.*



328 (71%) of patients with CF were followed-up compared to 824 (75%) of those with CF that were not followed-up after viral eradication **P=0.05**

Transaminase levels according to cofactors of liver disease progression

ALT remained elevated during the follow-up in 18 of 1152 (1.6%) patients with F1-F2 and CF compared to none of patient without CF.

In patients with F3 fibrosis stage:
During the follow-up, transaminase levels remained altered in 4% of patients with CF compared to none in those without CF.
AST levels at the end of treatment were significantly higher (6/186 =3.2%) in those who were defined as lost at follow-up by clinical centers (follow-up < 12 months) compared to those with an available follow-up (1/266 =0.4%) P=0.013

In patients with liver cirrhosis:
AST levels at the end of treatment were significantly higher (77/1599=4.8%) in those with CF compared to those without CF (3/285=1%) P=0.02. No statistical differences were observed for ALT levels post viral eradication in those with or without CF.

Outcomes (HCC, OLT, Death) following viral eradication in patients with F4/cirrhosis according to the presence of cofactors for liver disease progression

	Summary statistics	Total (n=2008)	Cofactors NO (n=296)	Cofactors YES (n=1712)	p value
HCC	%, n/Pts	7.8% (81/1887*)	3.9% (11/ 283)	4.4% (70/1594)	0.700
OLT	%, n/Pts	1.2% (23/1891)	0.7% (2/ 285)	1.3% (21/1606)	0.390
Death	%, n/Pts	2.9% (58/2008)	1.0% (3/ 296)	3.2% (55/1712)	0.037
Child Pugh class					
Improvement	%, n/Pts	63.6% (1277/2008)	61.8% (183/ 296)	63.9% (1094/1712)	0.561
Deterioration	%, n/Pts	36.4% (731/2008)	38.2% (113/ 296)	36.1% (618/1712)	
AST (<50) post therapy	%, n/Pts	95.6% (1802/1884)	98.2% (280/ 285)	95.2% (1522/1599)	0.02
AST (<50) post therapy	%, n/Pts	95.6% (1802/1884)	96.1% (274/ 285)	95.6% (1528/1599)	0.658

Mean follow-up 24 months (Range: 10-38months)

* Excluded patients with HCC at baseline

In 3 (0.6%) patients with CF and F3 fibrosis stage, as defined by elastometry prior to antiviral therapy, HCC was developed during the follow-up after viral eradication.

Predictive factors of HCC incidence*

	Univariate analysis n=1876 HR	95% CI	p	Cox Regression Analysis** n=1855 HR	95% CI	p
Gender						
F	reference			excluded		
M	1.45	0.91-2.32				
Age, yrs	1.07	1.04-1.09	<0.001	1.07	1.05-1.10	<0.001
Cofactors liver disease progression						
Cofactors NO	Reference			Did enter not in the model		
Cofactors YES	1.15	0.61-2.18	0.66			
Genotype						
Other	reference			reference		
Type 3	0.94	0.45-1.95	0.869	2.37	1.06-5.13	0.036
Decreased Albumin	0.83	0.71-0.97	0.021	1.2	1.2-1.43	0.029
Baseline INR	0.71	0.39-1.27	0.245	did enter not in the model		
Baseline Platelets count						
≥100,000	reference			did not enter in the model		
<100,000	1.59	1.02-2.46	0.039			

**Excluded patients with HCC before or during antiviral therapy N=63 patients*
***Stepwise selection was applied; INR, platelet count, transamanase levels and changes in Child Pugh score did not enter in the model and are not shown in the table.*

Predictive factors of Decompensated event in patients with F4/Cirrhosis

	Univariate Analysis n=1867 HR	95% CI	p	Cox Regression Analysis N=1867 HR	95% CI	p
Gender						
F	reference			reference		
M	1.03	0.74-1.42	0.877	1.18	0.84-1.66	0.333
Age, yrs	1.02	1.01-1.04	0.002	1.04	1.02-1.06	<0.001
Cofactors liver disease progression						
Cofactors NO	reference			did not enter in the model		
Cofactors YES	1.13	0.71-1.79	0.61			
Genotype						
Other	reference			did not enter in the model		
Type 3	1.34	0.83-2.17	0.235	did not enter in the model		
Baseline Albumin	0.81	0.72-0.90	0.0002	1.2	1.06-1.37	0.02
Baseline INR	1.95	1.40-2.71	<0.001	did not enter in the model		
Baseline Platelets count						
≥100,000	reference			Reference		
<100,000	2.94	2.09-4.16	<0.001	2.14	1.5-3.06	<0.001
Liver decompensation prior to treatment						
No	reference					
Yes	6.67	4.82-9.24	<0.001	5.91	4.22-8.27	<0.001

Outcomes (Decompensated Cirrhosis) following viral eradication in patients with F4/cirrhosis according to the presence of cofactors for liver disease progression

Decompensated Cirrhosis according to therapy timeline

Decompensated Cirrhosis	n	%
Never	1633	86.5%
At Baseline only	104	5.5%
At Baseline and After viral eradication	61	3.2%
After viral eradication only	90	4.8%
Totale	**1888 ***	

**Evaluated patients: F4/cirrhosis at baseline= 2008*
Of 120 patients the follow-up data were not available.
Available data of 1888 pt

During the follow-up 3.2% of patients with decompensated cirrhosis before treatment had a new episode of decompensation whereas in 4.8% an incident decompensation episode was registered.

Decompensated Cirrhosis according to the presence of cofactors for liver disease progression

	Decompensated at baseline YES	Cofactors NO	Cofactors YES	P value
Decompensated event post therapy	N pt: 165	N pt :26	N pt: 139	
	61 (40%)	7 (26.9%)	54 (38.8%)	0.248
	Decompensated at baseline NO	Cofactors NO	Cofactors YES	P value
	N pt: 1723	N pt : 259	N pt: 1464	
	90 (5.2%)	14 (5.4%)	76 (5.2%)	0.887

CONCLUSIONS

The presence of cofactors for liver disease progression is common in patients with HCV who received antiviral therapy in Italy. Most physicians did not follow EASL recommendations and interrupted follow-up in F0-F2 patients regardless of the presence of cofactors for liver disease progression. As indicated by EASL guidelines, since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT levels. Our data confirm no differences for ALT levels post viral eradication in those with or without cofactors for liver disease progression, however in patients with liver cirrhosis, AST levels, at the end of treatment were significantly higher in those with cofactors compared to those without cofactors. As suggested by EASL guidelines: Post-treatment surveillance for HCC must also be performed in patients with advanced fibrosis (METAVIR score F3) (Evidence B1). Our data confirm that patients who are diagnosed prior antiviral therapy as F3 liver fibrosis stage by elastography, should be followed up as those with liver cirrhosis after viral eradication in that possible underestimation of liver fibrosis stage and the residual risk of HCC development could not be ruled out. Cofactors of liver disease progression are associated with persistent post SVR transaminase elevations, but were not associated with higher incidence of HCC or liver related complications during a medium term follow-up of patients with cirrhosis after HCV viral eradication. Old age, lower albumin levels and low platelet's count, all surrogate markers of severe liver disease prior antiviral therapy, are independent predictors of liver disease progression despite viral eradication.

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