The PVT risk is still considerable after SVR among patients with cirrhosis.

Severity of liver disease remains the main determinant of PVT development.

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De-novo occurrence of portal vein thrombosis in patients with HCV-related cirrhosis after sustained virological response: medium to long term observations from the ongoing PITER cohort

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PITER
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1 Introduction

Achievement of sustained virological response (SVR) by direct-acting antiviral therapy (DAAs) in patients with cirrhosis (both compensated and decompensated) is associated with reduced risks of decompensation, liver-related mortality and hepatocellular carcinoma (HCC). In addition, SVR ameliorates portal hypertension, and may reverse hyper-coagulability driven by cirrhosis. However, an unexpected incidence of portal vein thrombosis (PVT) immediately after antiviral therapy has recently been reported.

2 Aim

Based on the prospective multicenter design of the ongoing PITER cohort, representative of HCV patients in care in Italy, we aimed to 1) determine the incidence of PVT in patients with HCV cirrhosis who achieved SVR after DAAs *vs* those who didn't and *vs* untreated patients; 2) investigate predictive factors for development of PVT in these patients.

3 Method

Study population: All consecutively enrolled patients in the PITER cohort diagnosed with liver cirrhosis independently by DAA therapy were evaluated. Patients with a previous diagnosis of PVT, previous liver transplantation or on the waiting list, were excluded. Neoplastic PVT were excluded from this analysis. IFN-free DAA-treated patients with at least a 12-weeks F.U. after the end of treatment were included. For treated patients, follow-up started when DAA therapy was finished. Untreated patients with at least F.U. after enrolment were included.
Statistical Analysis: The Mann-Whitney U test was used for continuous variables to assess differences between distribution, and the Chi-squared test was used to compare proportions. *De-novo* PVT occurrences were examined using Kaplan–Meier survival analyses and the log-rank test. Cox proportional hazard model was used to evaluate predictive factors independently associated with *de-novo* PVT adopting a forward stepwise selection, adding terms with p≤0.1 and removing those with p≥0.2. A propensity score was calculated to take into account the imbalance between the untreated group and the successfully treated group. A p value <0.05 was considered statistically significant. Statistical analysis was performed with STATA version 16.1 (StataCorp, College Station, TX, USA).

4 Results

PVT de-novo occurrence in DAA treated and untreated patients

Of overall 1626 consecutive patients with liver cirrhosis who undergone the antiviral therapy (median follow-up time was 35.6 months after EOT; IQR 23.3 - 44.3 months), 34 (2.1%) developed non-neoplastic PVT following DAA treatment. The two year PVT cumulative incidence rates were 0.7% for SVR patients and 6.4% for those who failed to achieve the SVR (p<0.001) (**Figure 1**). A total of 508 untreated patients with at least 1-year FU after enrolment and 1386 patients who achieved the SVR with the availability of values for each pre-treatment variables considered, were compared for PVT development. All the variables analyzed were well matched between the two groups after Inverse Probability Weighting (IPW) (Weighted SMD < 0.1) (data not shown).
Considering the EOT as the starting time point for treated patients and the enrollment date for untreated patients, in the first 36 months, there are 12 *de-novo* PVT diagnoses in the untreated patients, with a weighted incidence rate of 0.09% (CI95%: 0.05-0.18) and 15 new diagnoses in the successfully treated patients with an incidence rate of 0.04% (CI 95%: 0.02-0.06). Treated patients with SVR report a weighted HR=0.41 (CI 95% 0.18-0.93) p=0.033, which indicates that in the first 36 months following viral eradication, the PVT development risk is halved compared to the risk observed in untreated patients. The two year PVT cumulative incidence rates were 2.4% for the untreated patients and 0.8% in treated patients with SVR **(Figure 2).**

PVT cumulative incidence rates in cirrhotic treated patients by SVR

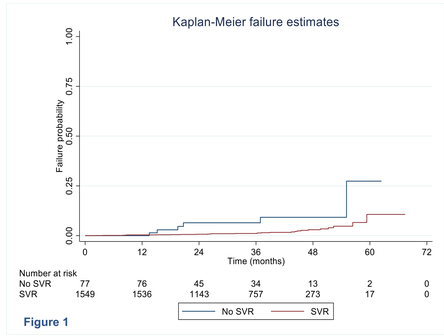

Figure 1

Baseline characteristics of cirrhotic DAA successfully treated patients by PVT occurrence

Of 1549 SVR patients, 28 (1.8%) experienced non-neoplastic PVT (median time of PVT occurrence was 33.8 months after EOT; IQR 17-45 months). Of them, 12 reported HCC (3 previous and 9 after achieving the SVR).

		No thrombosis (N=1521*)		Thrombosis occurrence (N=28*)			TOTAL (N=1549*)	
Epidemiological features		Median (IQR)		Median (IQR)		p**	Median (IQR)	
Age (years)		65 (56 - 72)		67 (58 - 71)		0.616	65 (56 - 72)	
		N.	%	N.	%	p***	N.	%
Sex	Male	842	55.4	13	46.4	0.346	855	55.2
	Female	679	44.6	15	53.6		694	44.8
BMI	Underweight-Normal	661	43.5	11	39.3	0.329	672	43.4
	Overweight	634	41.7	10	35.7		644	41.6
	Obese	226	14.9	7	25.0		233	15.0
Alcohol use	Never	1023	68.1	22	78.6	0.369	1045	68.3
	Current	153	10.2	3	10.7		156	10.2
	Past	326	21.7	3	10.7		329	21.5
HCV-genotype	1a	171	11.2	1	3.6	0.507	172	11.1
	1b	911	58.9	18	64.3		929	60.0
	2	219	14.4	6	21.4		225	14.5
	3	128	8.4	1	3.6		129	8.3
	Other	92	6.1	2	7.1		94	6.1
HIV+	Yes	55	3.6	1	3.6	0.990	56	3.6
	No	1466	96.4	27	96.4		1493	96.4
HBV Infection	Anti-HBc+/HBsAg+	16	1.1	0	0.0	0.675	16	1.0
	Anti-HBc+/HBsAg-	294	19.3	4	14.3		298	19.2
	No	1211	79.6	24	85.7		1235	79.7
Metabolic syndrome	Yes	207	13.6	2	7.1	0.321	209	13.5
	No	1314	86.4	26	92.9		1340	86.5
History of HCC	Yes	120	7.9	3	10.7	0.584	123	7.9
	No	1401	92.1	25	89.3		1426	92.1
Previous Interferon use	Yes	725	47.7	13	46.4	0.897	738	47.6
	No	796	52.3	15	53.6		811	52.4
Diabetes	Yes	345	22.7	9	32.1	0.237	354	22.9
	No	1176	77.3	19	67.9		1195	77.1
Clinical features		N.	%	N.	%	p***	N.	%
Platelets count	≤ 150,000/µL	1075	71.3	27	96.4	**0.003**	1102	71.8
	> 150,000/µL	432	28.7	1	3.6		433	28.2
Albumin (g/dL)	≤ 3.5	346	24.1	18	64.3	**< 0.001**	364	24.9
	> 3.5	1088	75.9	10	35.7		1098	75.1
Bilirubin (mg/dL)	≥ 1.1	460	31.3	20	71.4	**< 0.001**	480	32.0
	< 1.1	1012	68.8	8	28.6		1020	68.0
INR	≥ 1.1	737	51.4	20	71.4	**0.036**	757	51.8
	< 1.1	696	48.6	8	28.6		704	48.2
Liver Stiffness Measurement (kPa)	≥ 20	586	48.8	10	66.7	0.169	596	49.0
	< 20	615	51.2	5	33.3		620	51.0
FIB4	> 3.25	1025	68.5	25	89.3	**0.019**	1050	68.9
	≤ 3.25	471	31.5	3	10.7		474	31.1
Child-Pugh Class	A	1305	85.8	17	60.7	**< 0.001**	1322	85.3
	B	216	14.2	11	39.3		227	14.7
Previous decompensations	Yes	159	10.5	11	39.3	**< 0.001**	170	11.0
	No	1362	89.6	17	60.7		1379	89.0

PVT cumulative incidence rates in cirrhotic successfully treated *vs* untreated patients

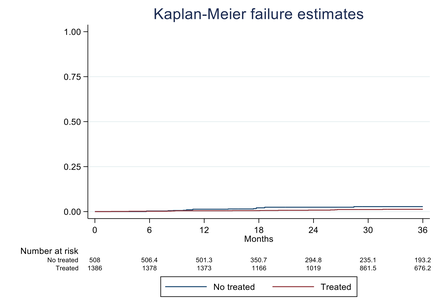

Figure 2

Pre-treatment variables associated with *de-novo* PVT occurrence in cirrhotic DAA successfully treated patients. Univariate and multivariate analysis.

Pre-treatment factors	Crude HR	95% CI	Adjusted HR*	95% CI
Age (increasing years)	1.02	0.98 - 1.06	1.02	0.97 - 1.06
Gender (ref. male)	1.39	0.66 - 2.93	1.38	0.64 - 2.97
BMI: overweight (ref. under-normalweight)	0.97	0.41 - 2.29		
obese (ref. under-normalweight)	2.33	0.90 - 6.04	2.18	0.89 - 5.32
Alcohol use: current (ref. never)	1.29	0.38 - 4.33		
past (ref. never)	0.44	0.13 - 1.46		
HCV-genotype (3 vs others)	0.43	0.06 - 3.15		
HCC	1.12	0.27 - 4.73		
Previous Interferon treatment	0.81	0.38 - 1.71		
Platelets (ref. >120,000/µL)	**9.48**	**1.29 - 69.78**	**3.56**	**1.03 - 12.33**
Albumin (ref. > 3.5 g/dL)	**5.75**	**2.65 - 12.47**	**2.66**	**1.15 - 6.15**
Bilirubin (ref. > 1.1 mg/dL)	**5.32**	**2.34 - 12.09**	**2.70**	**1.10 - 6.65**
INR (ref. < 1.1)	**2.44**	**1.07 - 5.55**		
Previous decompensation	**5.00**	**2.33 - 10.70**	2.17	0.96 - 4.86
Diabetes	1.64	0.64 - 3.73		

* Cox forward stepwise selection

5 Conclusions

The risk of *de-novo* non-neoplastic PVT in patients with cirrhosis who achieved the SVR is low and mainly related to the liver disease severity. PVT development following the SVR may identify patients with higher decompensation and mortality risks.

6 Acknowledgements

Authors wish to thank PITER collaborating group and all the clinical centers (available at www.progettopiter.it) which are involved in the study on a voluntary basis and Giampaolo La Terza (Medisoft Informatic Services) for Database maintainance and implementation

7 References

•LA Kondili, S Vella and PITER Collaborating Group. *Digestive and Liver Disease*. 2015; 47:741-743
•Zanetto A, Simioni P, Russo FP. *J Hepatol*. 2021; 74:967-968

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