Incidence and predictive factors of portal vein thrombosis in patients with HCV-related cirrhosis after sustained virological response: long term competing risk analysis in the PITER cohort

LA Kondili[1,2], A Zanetto[3,4], MG Quaranta[1], L Ferrigno[1], V Panetta[5], V Calvaruso[6], AL Zignego[7], MR Brunetto[8], G Raimondo[9], E Biliotti[10], D Ieluzzi[11], A Iannone[12], S Madonia[13], L Chemello[4], L Cavalletto[4], C Coppola[14], F Morisco[15], F Barbaro[3], A Licata[6], A Federico[16], M Viganò[17], M Persico[18], M Pompili[19], A Ciancio[20], F Piscaglia[21], L Chessa[22], A Giacometti[23], P Invernizzi[24,25], G Brancaccio[4], A Benedetti[23], L Baiocchi[26], I Gentile[15], N Coppola[16], G Nardone[15], A Craxì[6], FP Russo[3,4], PITER Collaborating Investigators (www.progettopiter.it)

[1]Istituto Superiore di Sanità, Rome, [2]UniCamillus, International Medical University in Rome, [3]University Hospital of Padua, [4]University of Padova, [5]L'altrastatistica srl, Consultancy & Training, Biostatistics office, Rome, [6]University of Palermo, [7]University of Florence, [8]University Hospital of Pisa, [9]University Hospital of Messina, [10]Policlinico Umberto I Hospital, Sapienza University of Rome, [11]University Hospital of Verona, [12]University of Bari, [13]Villa Sofia-Cervello Hospital, Palermo, [14]Gragnano Hospital, Gragnano (NA), [15]Federico II University, Naples, [16]University of Campania Luigi Vanvitelli, Naples, [17]San Giuseppe Hospital, Milan, [18]University of Salerno, Baronissi, [19]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, [20]University Hospital, Turin, [21]Sant'Orsola Malpighi Hospital, Bologna, [22]University Hospital, Monserrato, Cagliari, [23]Polytechnic University of Marche, Ancona, [24]University of Milano-Bicocca, Monza, [25]San Gerardo Hospital, Monza, [26]University of Tor Vergata, Rome

BACKGROUND & AIM

Patients with cirrhosis are at risk of portal vein thrombosis (PVT) [1]. Sustained virological response (SVR) by direct-acting antivirals (DAA) may reverse the hypercoagulable state associated with HCV cirrhosis [2]. However, whether DAA-driven SVR reduces the risk of PVT is unclear. We evaluated the incidence and predictive factors of *de-novo*, non-tumoral PVT in HCV cirrhosis after SVR.

METHODS

Patients

DAA-treated cirrhosis patients consecutively enrolled in the multicentric PITER cohort since 2014 were prospectively evaluated [3]. A group of untreated patients (n=448) were included as propensity-matched controls for PVT development. Patients previously diagnosed with PVT or those who either underwent or were awaiting liver transplantation were excluded.

Statistical analysis

Wilcoxon matched-pairs signed-rank test was used to assess the differences between matched pairs of observations.
A propensity score (PS) was calculated to account for the imbalance between the untreated and the successfully treated group. Long-term failure rates and overall and specific survival were estimated using weighted Kaplan-Meier curves, and comparisons were made with weighted Cox Regression. To evaluate the effect of demographic data and clinical variables on the risk of development of PVT, a Fine-Gray competing-risks regression model was applied, considering death or liver transplantation as competing event.

RESULTS

PVT incidence in untreated vs DAA-successfully treated patients

Propensity analysis was performed to balance untreated and DAA-successfully treated patients according to the severity of liver disease. Considering the end of treatment (EOT) as the starting time point for treated patients and the enrolment date for untreated patients, the two-year weighted cumulative incidence rate of PVT was 2.0% for untreated patients and 0.8% for patients who achieved the SVR.

The three-year weighted cumulative incidence rate of PVT was 2.4% for untreated patients and 1.3% for patients who achieved the SVR (**Figure 1**).

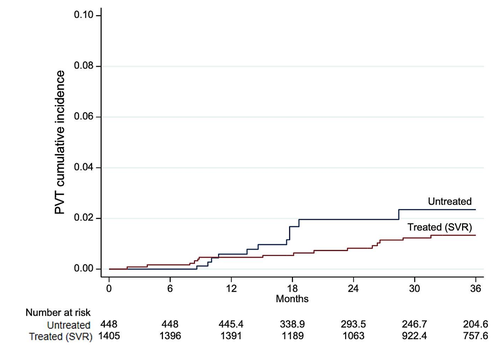


Figure 1. Weighted cumulative incidence of the development of PVT in DAA-successfully treated and untreated cirrhosis patients.

Baseline characteristics of the study population

During a median follow-up of 38.3 (IQR 25.1-48.7) months, of 1609 consecutive DAA-treated patients with cirrhosis who achieved the SVR, 32 (2.0%) developed PVT. The age, sex, BMI distribution, alcohol use, and presence of surrogate markers of metabolic syndrome were similar among patients who achieved the SVR and developed PVT and those who did not develop PVT. In contrast, a PLT count ≤120,000/µL, albumin level ≤3.5 mg/dL, bilirubin level >1.1 mg/dL, a history of liver decompensation, and ALBI, Baveno, FIB-4, and RESIST scores were all significantly different among patients who developed PVT vs. those who did not develop PVT (p<0.001) (data not shown), indicating greater severity of advanced liver disease in PVT patients.

Pre-treatment predictive factors for the occurrence of PVT

In a multivariable model, considering death or liver transplantation as competing risk events, pre-treatment ALBI grade>2 and presence of esophageal varices were independent PVT predictors (**Table 1**).

	Univariable			Multivariable*		
Pre-treatment factors	SubHR	95% CI	p	SubHR	95% CI	p
Sex (ref. male)	1.43	0.71-2.88	0.312			
Age (increasing years)	1.01	0.98-1.05	0.406			
Previous decompensation	4.80	2.38-9.68	<0.001			
Esophageal varices	13.21	5.37-32.54	<0.001	10.40	4.33-24.99	<0.001
Platelets (ref. >120,000/µL)	6.00	2.11-17.07	0.001			
ALBI (ref. grade 1)	7.15	2.18-23.41	0.001	4.32	1.36-13.74	0.013
INR (ref. < 1.1)	2.13	1.01-4.51	0.048			

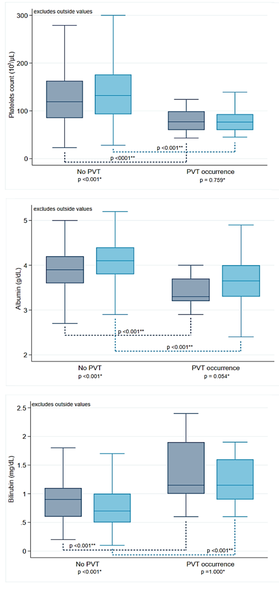
PVT events N=32
SubHR: SubHazard Ratio. CI: Confidence Interval.

* Stepwise Forward selection including variables with a p value <0.10 at univariable analysis.

Table 1. Pre-treatment variables associated with PVT occurrence in DAA successfully treated patients. Competing risk model results.

Prospective evaluation of factors associated with the severity of liver disease

There were significant variations in PLT, albumin, and bilirubin levels, evaluated within the first year after EOT, vs. pre-treatment values in patients who did not develop PVT (all p<0.001), whereas in those who developed PVT, all these parameters remained unchanged (p=0.759, p=0.054, and p=1.000, respectively).



* p value Wilcoxon signed-rank test comparisons between PRE-therapy and POST-therapy measurements
** p value Mann–Whitney rank-sum test comparisons between No PVT and PVT occurrence groups

Figure 2. Pre-treatment and post-treatment evaluation of factors associated with the severity of liver disease in patients with SVR.

Post-treatment predictive factors for the occurrence of PVT

ALBI grade>2, evaluated within the first year after EOT, and the presence of esophageal varices remained associated with *de-novo* PVT (**Table 2**).

	Univariable			Multivariable*		
Variables	SubHR	95% CI	p	SubHR	95% CI	p
Sex (ref. male)	1.09	0.44-2.73	0.847			
Age (increasing years)	1.03	0.98-1.10	0.293			
Previous decompensation	2.61	0.87-7.82	0.085			
Esophageal varices	14.16	4.58-43.79	<0.001	9.32	3.16-27.53	<0.001
Post-treatment factors						
Platelets (ref. >120,000/µL)	5.86	1.69-20.31	0.005			
ALBI (ref. grade 1)	9.56	2.75-33.14	<0.001	5.50	1.67-18.13	0.005

PVT events N=18
SubHR: SubHazard Ratio. CI: Confidence Interval.

* Stepwise Forward selection including variables with a p value <0.10 at univariable analysis.

Table 2. Post-treatment variables associated with PVT occurrence in DAA successfully treated patients. Competing risk model results.

CONCLUSIONS

Achieving SVR by DAA showed a reduced *de-novo* PVT development in patients with cirrhosis.

Patients with more advanced liver diseases before DAA therapy and those in whom liver function did not improve significantly within the first year after the HCV elimination remain at *de-novo* PVT risk.

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DISCLOSURES

Nothing to disclosure

CONTACT INFORMATION

Prof. Loreta Kondili. Center for Global Health,
Istituto Superiore di Sanità, Rome, Italy.
Email: loreta.kondili@iss.it