

NONTUMORAL PORTAL VEIN THROMBOSIS IN PATIENTS WITH HEPATITIS C VIRUS AND SUSTAINED VIROLOGICAL RESPONSE - A FURTHER CHALLENGING CONSEQUENCE OF LIVER CIRRHOSIS

Laura Huiban^{1,2}, C. Stanciu^{1,2}, Cristina Muzica^{1,2*}, Irina Girleanu^{1,2}, T. Cuciureanu^{1,2}, R. Nastasa^{1,2}, Ermina Stratina^{1,2}, S. Zenovia^{1,2}, R. Stafie^{1,2}, A. Rotaru^{1,2}, H. Minea^{1,2}, Oana Petrea^{1,2}, Ana-Maria Singeap^{1,2}, C. Sfarti^{1,2}, S. Chiriac^{1,2}, Camelia Cojocariu^{1,2}, Anca Trifan^{1,2}

“Grigore T. Popa” University of Medicine and Pharmacy, Iasi, Romania

Faculty of Medicine

1. Department of Medical Specialties (I)

“Sf. Spiridon” County Clinical Emergency Hospital, Iasi, Romania

2. Institute of Gastroenterology and Hepatology

*Corresponding author. E-mail: lungu.christina@yahoo.com

NONTUMORAL PORTAL VEIN THROMBOSIS IN PATIENTS WITH HEPATITIS C VIRUS AND SUSTAINED VIROLOGICAL RESPONSE-A FURTHER CHALLENGING CONSEQUENCE OF LIVER CIRRHOSIS (Abstract): The sustained virologic response (SVR) achieved by most patients treated with direct acting antivirals (DAAs) involves multiple benefits such as regression of fibrosis and improvement in liver function. However, DAAs therapy doesn't eliminate the risk of thrombotic events. The **aim** of our study was to assess the prevalence of nontumoral portal vein thrombosis (PVT) after SVR and identification of risk factors associated with this complication. **Material and methods:** We retrospective analyzed a cohort of patients with HCV-related liver cirrhosis treated with paritaprevir/ritonavir, ombitasvir and dasabuvir (PrOD) ± ribavirin and ledipasvir/sofosbuvir (LED/SOF) ± ribavirin for 12/24 weeks, in a gastroenterology center from Romania, between October 2015 and December 2018. All patients with presumption of PVT were evaluated by abdominal ultrasound and confirmed by CT scan. **Results:** The study included 730 patients treated with DAAs, of which 35 were diagnosed with non-malignant PVT after-SVR (15 men and 20 women, mean age 57.86 ± 7.068 years), corresponding to a prevalence of 4.8%. The mean time from SVR to complication was 290.00 ± 116.639 days. Most patients with non-tumoral PVT after-SVR received LED/SOF (71.4%), while the rest received PrOD (28.6%). Twenty-four patients (68.6%) diagnosed with acute PVT and 11 patients (31.4%) with chronic PVT. During the study, an improvement in liver function was observed, with an improvement in the Child-Pugh and MELD score at the time of SVR; the evolution changes slightly at the 48-week assessment, with a slight increase in the proportion of patients with Child B and MELD ≥ 15. **Conclusions:** Occurrence of non-malignant PVT in patients with HCV-related liver cirrhosis treated with DAAs correspond to the natural evolution of the cirrhotic patient. **Keywords:** CHRONIC HEPATITIS C INFECTION, NONTUMORAL PORTAL VEIN, THROMBOSIS, SUSTAINED VIROLOGICAL RESPONSE, DIRECT-ACTING ANTIVIRALS THERAPY, LIVER CIRRHOSIS.

The sustained virologic response (SVR) achieved by most patients treated with direct-acting antivirals (DAA) involves

multiple benefits such as regression of fibrosis, reduction of portal hypertension, and improvement of liver function (1,2). In

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

addition to the hepatic benefits of the virological cure mentioned, successful eradication of the C virus indirectly leads to the reversal of the hypercoagulable status by lowering procoagulant factors as close to normal parameters as possible, leading to a significant decrease in thrombotic complications (3, 4).

The long-term impact of sustained virological response after direct-acting antivirals on hypercoagulability associated with C viral liver cirrhosis is unknown. Up to this moment, there are few information regarding the improvement of coagulation status in patients treated with antivirals. There is a possibility that the safety profile of direct vascular antivirals may be incorrectly estimated due to the fact that there is no adequate reporting of the actual incidence of arterial and venous thrombotic events in clinical trials. However, an unexpected incidence of portal vein thrombosis (PVT) immediately after treatment with direct antivirals was recently reported (5).

Chronic viral hepatitis C (HCV) is itself associated with an increased risk of thromboembolic complications due to thrombocytopenia, low antithrombin III (ATIII) concentration, and the presence of antiphospholipid antibodies, which predisposes to arterial and venous thrombosis (6). In addition, an increase in platelet aggregation has been observed in patients with chronic HCV infection and advanced fibrosis, a phenomenon that could explain the occurrence of thrombotic events in these patients (6).

The incidence for any type of thromboembolic event reported by Enger *et al.* in a large study was 561.1 per 10,000 person/years in cirrhotic patients and 249.7 per 10,000 person/years for the control group (7). The main thrombotic complications

reported in this study that could occur in a cirrhotic patient were deep vein thrombosis, portal vein thrombosis, pulmonary thromboembolism, stroke, and acute coronary syndrome, but most studies focused on non-malignant PVT, which is seen the most frequent.

A reduced number of studies have attempted to evaluate the impact of direct antiviral therapy on coagulation and the main risk factors for the development of thrombotic events in cirrhotic patients treated with direct antivirals and SVR. The majority included thrombotic events such as non-malignant PVT and the one of neoplastic origin that is most often associated with hepatocarcinoma, in which the thrombotic mechanism is different (4,5,8).

The research of Tripodi *et al.* (3) and Russo *et al.* (4), proved for the first time that DAA treatment in patients with C viral liver cirrhosis resulted in improvement of pro- and anticoagulant status in patients who have acquired SVR. It does not substantially alter their balance but makes it more stable and less likely to be disturbed, as was supposed before treatment.

The main suspected risk factor for the occurrence of thrombosis after SVR in these few cases is liver fibrosis, which remains elevated in some of the patients treated with antivirals, a fact that is indirectly reflected on the degree of portal hypertension, mechanisms responsible for venous stasis in port system level with the risk of non-tumoral portal vein (9,10,11).

Thus, this study aimed to evaluate the prevalence of non-malignant portal vein thrombosis in patients with chronic HCV infection treated with interferon-free antivirals, and whether the development of PVT de novo is a reflection of the natural history of cirrhosis in patients with long-

term viral infection or is a consequence of DAA therapy.

MATERIAL AND METHODS

We performed a retrospective study in which we included patients diagnosed with compensated and decompensated viral liver cirrhosis C, randomly selected, to receive treatment with direct antivirals (Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir ± Ribavirin or Sofosbuvir/Ledipasvir ± Ribavirin) for 12/24 weeks, admitted to the Institute of Gastroenterology and Hepatology Iași, Romania, between October 2015 and December 2018. Additionally, they were considered inclusion criteria presence of non-malignant PVT. All patients were clinically and paraclinically evaluated at the time of admission; socio-demographic data, personal antecedents and symptoms were evaluated and recorded for all patients. The diagnosis of cirrhosis was based on clinical, biological and imaging data according to international guidelines. The diagnosis of viral C infection was suspected by anti-HCV Ab positivity and confirmed by HCV-RNA, the detection limit being 15 IU/mL. Sustained virologic response was defined as undetectable HCV-RNA level 12/24 weeks after completion of direct antiviral treatment.

The patients were followed for 3 years, and the data were collected as follows: at the initiation of treatment with direct antivirals (baseline), at the end of antiviral treatment (EOT), 3 months after completion of antiviral treatment (SVR12), 48 weeks after obtaining SVR12, 3 years after obtaining SVR12, on emergency admission in the event of a thrombotic complication after the period of antiviral treatment.

Blood samples for biochemical and immunological evaluations were collected at

scheduled visits. At the same time, an additional amount of blood was collected to perform coagulation tests at the time of diagnosis of non-malignant PVT. Two vacutainers of whole blood containing 1/10 volume of sodium citrate as an anticoagulant were taken, each vacutainer having a capacity of 2.7 mL. Blood samples were centrifuged for 15 minutes at 2500xg/min and plasma was collected and stored in 0.5 mL devices and subsequently frozen at -80°C until examination. Processing of biological samples was performed after thawing the plasma at 37°C for 5 minutes.

Portal vein thrombosis was diagnosed using a Philips HD11XE ultrasound machine equipped with a 3.5 MHz convex probe and was confirmed by contrast-enhanced computed tomography. Ultrasound PVT was defined as the presence of hyperechoic material within the portal vein or its branches. The portal cavernoma was defined by the presence of periportal collateral circulation, with the role of short-circuiting the thrombosed area. Portal vein thrombosis was defined as partial if the thrombus occupied less than 90% of the vessel lumen and complete when the thrombus obstructed more than 90% of the vessel. Portal vein thrombosis was considered acute in the context where before the examination the patient showed no signs of PVT, and at the time of diagnosis associated symptoms such as: abdominal pain, onset or worsening of ascites, variceal bleeding, or hepatic encephalopathy.

To check the patients who were a part of our inquiry for liver fibrosis we used the FibroScan® 520 compact model (Echosens, Paris, France) equipped with the M- (normal) or XL- (obese) probe. Firstly, the inspection was performed using an M-

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

probe with a 3.5 MHz transducer frequency. Then, the XL probe (2.5 MHz) was used if the distance between the skin and the liver capsule was higher than 25 mm. If 10 acquisitions were made with an interquartile interval not exceeding 30%, reliable measurement was determined to have occurred. The cut-offs for liver stiffness measurements (LSM) values were: 5.6 kPa for mild fibrosis (F1), 7.1 kPa for significant fibrosis (F2), 9.5 kPa for advanced fibrosis (F3), and 12.5 kPa for cirrhosis (F4).

Statistical processing was carried out using *Microsoft Excel* and *SPSS version 28* (Inc., Chicago, IL) programs. While categorical variables were expressed as absolute values and percentages, continuous variables with normal distributions were expressed as mean SD. To compare categorical data, the Chi-square test was employed. To compare the arithmetic means of a parameter analyzed in two samples, we used the t-Student test. We employed non-parametric tests, such as the Mann-Whitney U test, and the Kolmogorov-Smirnov test to determine whether the data distributions were normal. A *p*-value of 0.05 was used to determine the statistical significance of the results. When both variables were binary, we also calculated the corresponding OR (Odds Ratio) risks - the measure of the association between the presence of a risk factor and the occurrence of an event; these risks were calculated both in absolute value and as a 95% confidence interval.

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki, the protocol being explained in detail to all patients. Informed consent for participation in the study was obtained from all patients and/or their relatives.

RESULTS

General characteristics of the study population

During the study period, 730 patients with HCV liver cirrhosis were treated with DAAs therapy, of which 35 were diagnosed with non-malignant PVT, corresponding to a total incidence of 4.8%. The mean age of patients with non-malignant PVT was 57.86 ± 7.06 , the female gender being prevalent (57.1%), and patients came equally from urban or rural areas (51.4% vs. 48.6%). The mean time from SVR to complication was 290.00 ± 116.639 days, with a minimum of 74 days and a maximum of 450 days. The majority of patients with post-SVR PVT received LED/SOF (71.4%), while the rest received PrOD (28.6%). The study group consisted of 24 patients (68.6%) diagnosed with acute PVT and 11 patients (31.4%) with chronic PVT; most patients diagnosed with acute PVT associated partial occlusion of the portal vein (19 patients - 79.2%) with occlusion at the level of the trunk (15 patients - 62.5%). Half of the patients treated with antivirals were included in the Child C category (45.7%), just under a third were Child B (31.4%), and almost a quarter of patients were in the Child A category (22.9%), with no statistically significant differences between MELD score values. Among patients with PVT post-SVR, 22.9% did not have esophageal varices at the time of inclusion in the treatment, the number of patients with small and large esophageal varices being almost balanced (37.1% in the first case and 40.0% in the second). All patients presented various types of comorbidities: essential hypertension - 35 patients (100%), type 2 diabetes - 24 patients (68.57%), obesity - 12 (34.3%), psychiatric - 6 (17.1%), and neoplastic antecedents - 2 (5.7%) (tab. I).

TABLE I.
Baseline characteristics of patients with PVT - post SVR

Parameters	PVT - post SVR n=35
Age (years)	57.86 ± 7.068
Sex	
male, n (%)	15 (42.9%)
female, n (%)	20 (57.1%)
Environment	
urban, n (%)	18 (51.4%)
rural, n (%)	17 (48.6%)
Treatment	
LED/SOF	25 (71.4%)
PrOD	10 (28.6%)
Type PVT	
acute PVT	24 (68.6%)
chronic PVT	11 (31.4%)
Child-Pugh class	
class A, n (%)	8 (22.9%)
class B, n (%)	11 (31.4%)
class C, n (%)	16 (45.7%)
MELD score	
< 15	15 (42.9%)
≥ 15	20 (57.1%)
Esophageal varices	
absences	8 (22.9%)
small	13 (37.1%)
large	14 (40.0%)
Comorbidities	
Essential hypertension	35 (100%)
Type 2 diabetes	24 (68.57%)
Obesity	12 (34.3%)
Psychiatric	6 (17.1%)
Neoplastic antecedents	2 (5.7%)

Evolution of liver function and the degree of liver fibrosis in patients with non-malignant PVT post-SVR during the follow-up

Over the course of the study, an improvement in liver function was observed during antiviral treatment, with improvement of the Child-Pugh score and MELD at the time of SVR (45.7% CP class A, 54.3% CP class B, 100% patients with MELD

score < 15). The evolution changes at the 48-week assessment, with a slight increase in the proportion of patients in Child B class (68.6%). At the 3-year assessment/or at the occurrence of the thrombotic event, however, a significant deterioration of liver function was observed compared to the initial situation (62.9% CP class B, 37.1% CP class C; 11.4% MELD <15, 88.6% MELD ≥15) (figs. 1, 2).

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

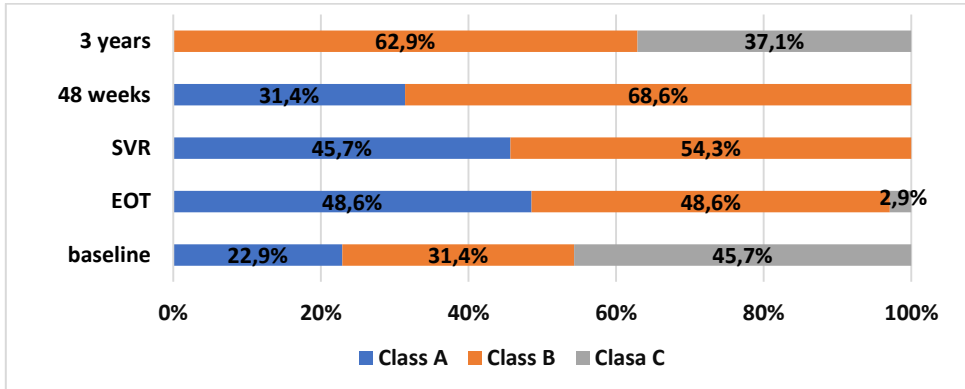


Fig. 1. Evolution of the Child-Pugh score during follow-up in patients with PVT post-SVR

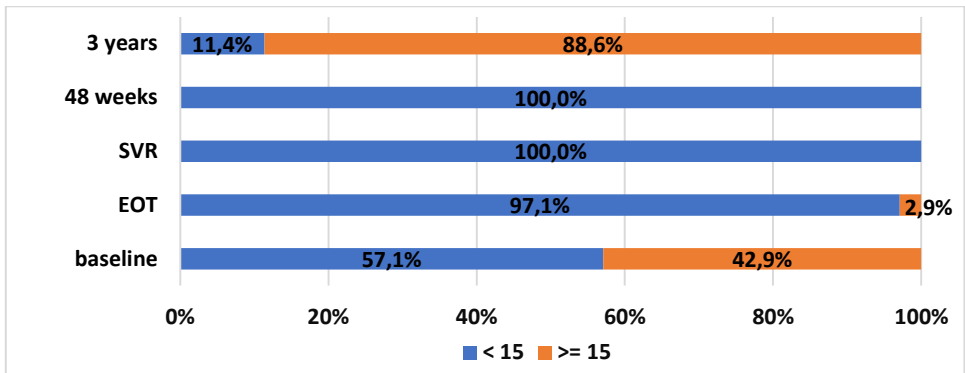


Fig. 2. Evolution of the MELD score during follow-up in patients with PVT post-SVR

Among the patients who achieved SVR with a pre-treatment CPT score ≥ 6 points, 23 (65.71%) showed an improvement in CPT score at the end of treatment (EOT). Among patients whose CPT score decreased ≥ 1 point, the cumulative incidence of non-tumoral PVT was 0%, 2.6%, and 6.5% at 1, 2, and 3 years, respectively, after the end of antiviral therapy, while the rates in those without a decrease in CPT were 8%, 10.8%, and 10.8%. Although the difference did not reach statistical significance (sHR: 0.454 (95% CI: 0.01-2.18; $p = 0.331$), the incidence of non-tumoral PVT was lower in patients who had an improvement in liver function during treat-

ment, justifying the consideration of liver function pre/post - treatment as risk factors for the development of non-tumoral PVT.

In the case of the variation in the degree of liver fibrosis, a similar process is observed, with a significant decrease in Fibroskan values when evaluating SVR (19.30 kPa from 31.23 kPa to baseline), with the same descending trend at 48 weeks (16.81 kPa) and 3 years (18.21 kPa), but with higher values >12 kPa.

Regardless of whether SVR implies improvement of the liver function, the highest risk of non-tumoral PVT remained in patients with advanced liver disease. Comparative distribution by Child-Pugh classes

of patients with PVT - post SVR: 22.9% patients with Child A, 31.4% patients with Child B, and 45.7% patients with Child C.

Risk factors for non-malignant PVT post-SVR in patients treated with DAA
 Among the qualitative parameters evalu-

ated as risk factors for the occurrence of non-malignant PVT in patients with HCV liver cirrhosis treated with antivirals in the studied group, the presence of type II diabetes, ascites, hepatic encephalopathy and the decompensated status of liver disease reached the threshold of statistical significance (tab. II).

TABLE II.
Comparative study of qualitative parameters monitored in patients with PVT post-SVR

		PVT				Total		Pearson χ^2	p
		Yes		No		N	%		
		N	%	N	%				
Sex	Male	15	42.9%	283	40.7%	298	40.8%	0.06	0.802
	Female	20	57.1%	412	59.3%	432	59.2%		
Age \geq 65 years	Yes	6	17.1%	226	32.5%	232	31.8%	3.63	0.057
	No	29	82.9%	469	67.5%	498	68.2%		
Obesity	Yes	12	34.3%	181	26.0%	193	26.4%	1.16	0.281
	No	23	65.7%	514	74.0%	537	73.6%		
Comorbidities	Yes	35	100.0%	684	98.4%	719	98.5%	0.56	0.453
	No	0	0.0%	11	1.6%	11	1.5%		
Type 2 diabetes	Yes	35	100.0%	577	83.0%	612	83.8%	7.08	0.008**
	No	0	0.0%	118	17.0%	118	16.2%		
Esophageal varices	Yes	27	77.1%	478	68.8%	505	69.2%	1.09	0.296
	No	8	22.9%	217	31.2%	225	30.8%		
Ascites OR: 8.086 CI 95% (4.01-16.30)	Yes	19	54.3%	89	12.8%	108	14.8%	45.48	0.000**
	No	16	45.7%	606	87.2%	622	85.2%		
Non-selective beta blocker	Yes	0	0.0%	38	7.4%	38	7.3%	0.64	0.542
	No	8	100.0%	473	92.6%	481	92.7%		
Cirrhosis OR: 6.825 CI 95% (3.39-13.70)	Decompensated	19	54.3%	103	14.8%	122	16.7%	37.28	0.000**
	Compensated	16	45.7%	592	85.2%	608	83.3%		
Hepatic encephalopathy OR: 8.643 CI 95% (3.92-19.05)	Yes	11	31.4%	35	5.0%	46	6.3%	39.31	0.000**
	No	24	68.6%	660	95.0%	684	93.7%		

The analysis of quantitative parameters compared between patients with non-malignant PVT and the rest of cirrhotic patients treated with antivirals, revealed statistically significantly increased values

for PT, INR, aPTT, ASAT, ALAT, BT, MELD score, and statistically significant values low for platelets, AP and albumin in patients with non-malignant PVT post-SVR (tab. III).

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

**TABLE III.
Comparative study of quantitative parameters
monitored in patients with PVT post-SVR**

PVT		N	Media	SD	Median	Minimum	Maximum	p
Platelets	Yes	35	106428.57	19122.33	110000.00	62000	140000	0.003**
	No	693	136566.09	62960.22	124000.00	16000	475000	
PT	Yes	35	16.76	1.38	16.80	14.60	19.60	0.000**
	No	661	13.48	2.65	12.90	8.30	46.80	
AP	Yes	35	65.17	4.40	65.00	55.0	74.0	0.000**
	No	613	82.94	16.13	85.00	15.0	115.0	
INR	Yes	35	1.88	0.55	2.01	0.77	2.90	0.000**
	No	685	1.35	0.51	1.17	0.82	7.79	
aPTT	Yes	35	44.20	5.30	42.00	39.00	58.00	0.000**
	No	695	32.08	7.23	31.00	22.00	64.00	
ASAT	Yes	35	218.31	73.55	214.00	116.00	359.00	0.000**
	No	695	121.34	79.28	98.00	9.00	625.00	
ALAT	Yes	35	205.48	74.91	204.00	110.00	380.00	0.000**
	No	695	113.80	69.19	93.00	16.00	449.00	
BT	Yes	35	2.34	0.80	2.39	1.18	5.45	0.000**
	No	655	1.23	0.72	1.05	0.16	4.76	
Albumin	Yes	35	2.88	0.70	3.09	0.81	4.22	0.000**
	No	686	3.87	0.60	3.90	1.31	5.29	
MELD	Yes	35	13.71	4.66	12.00	7	21	0.000**
	No	692	10.22	3.45	9.00	6	21	

PT, prothrombin time; AP, prothrombin activity; INR, international normalized ratio; aPTT, activated partial thromboplastin time; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BT, total bilirubin

DISCUSSION

One of the triumphs of medical therapy in the last two decades, proved by the effectiveness of direct-acting antivirals, is firmly proven by achieving SVR in over 95% of treated patients (12) and which was associated with reducing the progression of chronic hepatitis to cirrhosis, decreasing the risk of decompensation liver and portal hypertension complications, decreasing the need for liver transplantation and decreasing

the risk of hepatocellular carcinoma (HCC) (2). Despite effective treatments related to HCV, in addition to the complications and characteristics specific to each progressive stage of liver disease, thromboembolic events could be associated even in patients responding to antiviral treatment.

Non-malignant PVT, an intensely debated topic in recent years, represented the most frequent thromboembolic complica-

tion that might occur in the natural course of liver cirrhosis. The prevalence of PVT varies according to the degree of liver failure and the presence of HCC, being up to 1% in patients with compensated liver cirrhosis, reaching 8% - 25% in liver transplant candidates and 40% in patients with HCC (13). In our study the incidence of non-malignant PVT post-SVR was 4.8%, higher than that reported to date in other studies (4). Stine JG *et al.* reported the experience of seven patients on DAA treatment, followed in a 4-year prospective study, who developed non-malignant PVT (one case with total PVT and six cases with partial PVT) after obtaining SVR (8). During this period 461 subjects were treated with direct antivirals, of which 54.8% (231 patients) were cirrhotic. The incidence of PVT post-SVR was 3% which, although lower than the incidence rates reported in the literature, is not expected given that most patients were not decompensated. At the same time, Russo *et al.* (4) identified 2 cases of non-malignant PVT in a prospective study that included 58 patients treated with antivirals and with SVR, which corresponds to an incidence of 3.44%, lower than that identified in our study. Mandorfer M *et al.* recently reported an incidence of non-malignant PVT of 2.8% in a prospective study of 354 patients with HCV and SVR cirrhosis, much lower than previously reported (5).

The pathogenesis of thrombosis is multifactorial, based on the elements of Virchow's triad: vascular stasis, endothelial injury and hypercoagulability (14, 15, 16). Numerous pieces of evidence stated the fact that the C virus hepatitis could activate hemostasis, and the endothelial damage, the inflammation described at the level of the vascular wall, the changes in the level of the hepatic microcirculation as well as

the alteration of the coagulation parameters determined by the HCV infection represent factors that contribute to the occurrence of thrombotic events in advanced liver disease (17).

The majority of patients with non-malignant PVT post-SVR were classified as Child-Pugh B (31.4%) and Child-Pugh C (45.7%), with Child-Pugh A being in the minority (22.9%). Also, most patients with non-malignant PVT post-SVR had a MELD score ≥ 15 at the time of initiation of antiviral treatment. These results obtained in our study were different compared to the data reported in the whole literature. The prospective study by Stine *et al.* (8) included only patients with compensated HCV liver cirrhosis (Child A), which was why the occurrence of PVT post-SVR was an unexpected event, appearing on the background of a perfectly compensated field. In contrast, Russo *et al.* (4) detected non-malignant PVT in 2 patients who were with Child B, a similar situation to the cases reported by Mandorfer B *et al.* (5), where non-malignant PVT post-SVR was found in patients with decompensated liver cirrhosis.

In the studied group, the gender distribution was balanced, with the female gender having a higher weight (57.1%). This distribution of cases is also consistent with the epidemiological data from the specialized literature published for Romania, which reports a higher prevalence of HCV infection in the female sex (18), a fact that justified the larger number of women who addressed for evaluation to initiate antiviral treatment. The mean age of patients with nonmalignant PVT treated with antivirals was 57.86 ± 7.068 , similar to the age of patients who experienced thrombotic events reported in other studies (4, 5, 8).

The mean time from SVR to complication was 290.00 ± 116.639 days, with a

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

minimum of 74 days and a maximum of 450 days. Time to PVT was similar to Stine *et al.* (8) at 272 ± 204 days, with 5 patients diagnosed with PVT < 365 days after obtaining SVR. Mandorfer *et al.* (5) showed that non-tumoral PVT in responders was detected during a mean follow-up of 37.1 months, whereas 8 (4.5%) of patients without SVR were diagnosed with malignant PVT during a mean follow-up of 42.2 months. The shortest period was reported by Russo *et al.* (4), the occurrence of the thrombotic event being at the time of SVR12. A unique case was reported by Garg H *et al.* (19) who described 2 clinical cases with acute nonmalignant PVT discovered during antiviral treatment in 2 patients who received treatment with sofosbuvir and ribavirin. The mechanism underlying these events was interpreted as a simple drug reaction, these antivirals exhibiting idiosyncratic (type B) drug reactions, but they are rare and unpredictable.

Various studies on the efficacy of DAA treatment have shown that achieving SVR in patients with viral hepatitis C cirrhosis was associated with improved MELD and Child-Pugh scores, which reflect improved liver synthesis function (20, 21, 22, 23), a hypothesis that was also confirmed in our study. At the initial assessment, of the 35 patients with PVT post-SVR, almost half (45.75%) were in Child C, one third were in Child B (31.4%), and the remaining 22.9% were part of the Child A. The situation improved along the way, so that at the end of the treatment only one patient (2.9%) remained classified in the Child C, the others being classified in equal percentages in the Child A classes and B, evolution that remained favorable also at SVR12. The results obtained in our study are also confirmed by Gentile *et al.* (24) in an Italian multicenter prospective study of

89 patients with decompensated HCV and responders to antiviral treatment, in whom the rate of change to Child A was 62% 24 weeks after obtaining SVR.

In the present study, the process was also similar to the evolution of the MELD score: at the initial assessment, the proportions of patients with a MELD score below the threshold value of 15 and above it were relatively balanced, with a slight superiority for patients with a MELD score < 15 (57, 1%). At the EOT, the situation improved significantly, only one patient (2.9%) remained with the MELD score > 15, a situation that remained favorable at the time of SVR12. In the SOLAR-1 and SOLAR-2 studies, patients with genotype 1 or 4 decompensated HCV cirrhosis who received DAA showed improvement in both MELD and Child-Pugh (25, 26). Similar results were also reported by Poordad F *et al.* (27) in the ALLY-1 study, where all patients with decompensated cirrhosis and SVR, regardless of genotype, showed improvement in liver function. On the other hand, Marco and Calvaruso showed that in patients with decompensated cirrhosis (ascites, hepatic encephalopathy, bleeding from variceal rupture) treated with antivirals, obtaining SVR does not improve liver dysfunction or mortality (28).

Similarly, in the case of the variation in the degree of liver fibrosis, a similar process was observed, with a significant decrease in Fibroscan values at the SVR assessment, with the same downward trend at 48 weeks and 3 years, but with higher values >12 kPa. These results attest to the fact that there is a risk of thrombotic complications in the portal system even after achieving SVR, the persistence of portal hypertension favoring intravascular blood stasis being considered a key element in the occurrence of portal vein thrombosis (29, 30,

31, 32, 33, 34).

Regardless of whether SVR implies improvement of the liver function, the highest risk of non-tumoral PVT remained for patients with advanced liver disease (Child C). The results of our study are confirmed by Mandorfer *et al.* who observed that an elevated Child-Pugh score was the only independent risk factor for the development of non-malignant PVT post-SVR, with patients with a Child A score having the lowest risk (5).

Among the qualitative parameters evaluated as risk factors for the occurrence of non-malignant PVT in patients with HCV liver cirrhosis treated with antivirals, the presence of type II diabetes, ascites, hepatic encephalopathy and the decompensated status of liver disease reached the threshold of statistical significance. Quantitative parameters correlated as risk factors with non-malignant PVT in the studied group were increased BT and MELD score values, low albumin values, but also the persistence of an increased degree of post-SVR liver fibrosis. Age over 65 years, male gender, obesity and NSBB treatment were not risk factors in the study group. Stine *et al.* mentioned that patients with HCV cirrhosis treated with antivirals have a high risk of developing non-malignant PVT post-SVR, in the context where the 7 patients who developed a thrombotic complication were with Child A (8). This risk is independent of the value prothrombin time, INR or platelet count, the risk of PVT be-

ing due rather as a reaction to an overcorrection of an already fragile coagulation balance in the cirrhotic patient.

CONCLUSIONS

Achieving SVR decreases the risk of decompensation among cirrhotic patients, but the risk for thrombotic events still remains. The severity of the liver damage is a risk factor for the occurrence of nonmalignant PVT post-SVR, the majority of patients who developed this complication being Child-Pugh C score. The persistence of liver fibrosis with higher values >12 kPa after obtaining SVR demonstrates the persistence of portal hypertension and implicitly, an increased risk for the occurrence of nonmalignant PVT, which is why these patients must continue to be carefully monitored according to the protocol. Future research should focus on personalizing post-SVR care based on individual risk of complications.

CONFLICT OF INTEREST AND FUNDING

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This article was published with the support of the project “Net4SCIENCE: Applied doctoral and postdoctoral research network in the fields of smart specialization Health and Bioeconomy”, project code POCU/993/6/13/154722.

REFERENCES

1. Lens S, Baiges A, Alvarado-Tapias E, *et al.* Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. *J Hepatol* 2020; 73(6): 1415-1424.
2. Ioannou GN, Feld JJ. What Are the Benefits of a Sustained Virologic Response to Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection?. *Gastroenterology* 2019; 156(2): 446-460.

Nontumoral portal vein thrombosis in patients with hepatitis C virus and sustained virological response - a further challenging consequence of liver cirrhosis

3. Tripodi A, D'Ambrosio R, Padovan L, *et al.* Evaluation of coagulation during treatment with directly acting antivirals in patients with hepatitis C virus related cirrhosis. *Liver Int* 2017; 37(9): 1295-1303.
4. Russo FP, Zanetto A, Campello E, *et al.* Reversal of hypercoagulability in patients with HCV-related cirrhosis after treatment with direct-acting antivirals. *Liver Int* 2018; 38(12): 2210-2218.
5. Mandorfer M, Turon F, Lens S, *et al.* Risk of non-tumoral portal vein thrombosis in patients with HCV-induced cirrhosis after sustained virological response. *Liver Int* 2021; 41(12): 2954-2964 / doi: 10.1111/liv.15009.
6. Nielsen NS, Jespersen S, Gaardbo JC, *et al.* Impaired Platelet Aggregation and Rebalanced Hemostasis in Patients with Chronic Hepatitis C Virus Infection. *Int J Mol Sci* 2017; 18(5): 1016.
7. Enger C, Forssen UM, Bennett D, Theodore D, Shantakumar S, McAfee A. Thromboembolic events among patients with hepatitis C virus infection and cirrhosis: a matched-cohort study. *Adv Ther* 2014; 31: 891- 903.
8. Stine JG, Prakash S, Northup PG. Portal vein thrombosis after hepatitis C eradication with direct acting antiviral therapy. *Liver Int* 2018; 38(1): 185-186.
9. Gîrleanu I, Trifan A, Stanciu C, Sfarti C. Portal vein thrombosis in cirrhotic patients - it is always the small pieces that make the big picture. *World J Gastroenterol* 2018; 24(39): 4419-4427.
10. Krassenburg LAP, Maan R, Ramji A, *et al.* Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. *J Hepatol* 2021; 74(5): 1053-1063.
11. Foster GR, Irving WL, Cheung MC, *et al.* Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; 64(6): 1224- 12231.
12. Stanciu C, Muzica CM, Gîrleanu I, *et al.* An update on direct antiviral agents for the treatment of hepatitis C. *Expert Opin Pharmacother* 2021; 22(13): 1729-1741.
13. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. *Gastroenterology* 2019; 156: 1582-1599.
14. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011; 365: 147-156.
15. Nowatari T, Murata S, Fukunaga K, Ohkohchi N. Role of platelets in chronic liver disease and acute liver injury. *Hepatol Res* 2014; 44(2): 165-172.
16. Periyah MH, Halim AS, Mat Saad AZ. Mechanism Action of Platelets and Crucial Blood Coagulation Pathways in Hemostasis. *Int J Hematol Oncol Stem Cell Res* 2017; 11(4): 319- 327.
17. González-Reimers E, Quintero-Platt G, Martín-González C, Pérez-Hernández O, Romero-Acevedo L, Santolaria-Fernández F. Thrombin activation and liver inflammation in advanced hepatitis C virus infection. *World J Gastroenterol* 2016; 22(18): 4427-4437.
18. Trifan A, Stanciu C, Gheorghe L, *et al.* Efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with ribavirin for the treatment of HCV genotype 1b compensated cirrhosis in patients aged 70 years or older. *Medicine (Baltimore)* 2017; 96(50): e9271.
19. Garg H, Gupta S, Anand AC, Rastogi R. Acute portal vein thrombosis associated with Sofosbuvir and Ribavirin use. *Austin Hepatol* 2017; 2(1): 1007.
20. Zeng H, Li L, Hou Z, Zhang Y, Tang Z, Liu S. Direct-acting Antiviral in the Treatment of Chronic Hepatitis C: Bonuses and Challenges. *Int J Med Sci* 2020; 17(7): 892-902.
21. Calvaruso V, Craxi A. Hepatic benefits of HCV cure. *J Hepatol* 2020; 73(6): 1548-1556.
22. Koh C, Heller T, Haynes-Williams V, *et al.* Long-term outcome of chronic hepatitis C after sustained virological response to interferon-based therapy. *Aliment Pharmacol Ther* 2018; 37(9): 887-894.
23. Moon AM, Green PK, Rockey DC, Berry K, Ioannou GN. Hepatitis C eradication with direct-acting anti-virals reduces the risk of variceal bleeding. *Aliment Pharmacol Ther* 2020; 51(3): 364-373.
24. Gentile I, Scotto R, Coppola C, *et al.* Treatment with direct-acting antivirals improves the clinical outcome in patients with HCV-related decompensated cirrhosis: results from an Italian real-life cohort (Liver Network Activity-LINA cohort). *Hepatol Int* 2019; 13(1): 66- 74.
25. Manns M, Fornis X, Samuel JD, *et al.* Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: preliminary results of the prospective solar 2 trial. *J Hepatol* 2015; 62: 187-188.

26. Charlton M, Everson GT, Flamm SL, *et al.* Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015; 149: 649-659.
27. Poordad F, Schiff ER, Vierling JM, *et al.* LO8: Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY1 study. *Hepatology* 2015; 62: S261-S262.
28. Di Marco V, Calvaruso V, Ferraro D, *et al.* Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. *Gastroenterology* 2016; 151: 130-139.
29. Pons M, Rodríguez-Tajes S, Esteban JI, *et al.* Non-invasive prediction of liver-related events in patients with HCV-associated compensated advanced chronic liver disease after oral antivirals. *J Hepatol* 2020; 72(3): 472-480.
30. Essa M, Sabry A, Abdelsameea E, Tharwa ES, Salama M. Impact of new direct-acting antiviral drugs on hepatitis C virus-related decompensated liver cirrhosis. *Eur J Gastroenterol Hepatol* 2019; 31(1): 53-58.
31. Masetti C, Lleo A, Colombo M, Colombo M, Aghemo A. Postsustained Virological Response Management in Hepatitis C Patients. *Semin Liver Dis* 2020; 40(3): 233-239.
32. Ogasawara N, Saitoh S, Akuta N, *et al.* Advantage of liver stiffness measurement before and after direct-acting antiviral therapy to predict hepatocellular carcinoma and exacerbation of esophageal varices in chronic hepatitis C. *Hepatol Res* 2020; 50(4): 426- 438.
33. Mendizabal M, Piñero F, Ridruejo E, *et al.* Disease Progression in Patients With Hepatitis C Virus Infection Treated With Direct-Acting Antiviral Agents. *Clin Gastroenterol Hepatol* 2020; 18(11): 2554-2563.
34. Cheng CH, Chu CY, Chen HL, *et al.* Direct-acting antiviral therapy of chronic hepatitis C improves liver fibrosis, assessed by histological examination and laboratory markers. *J Formos Med Assoc* 2021; 120(5): 1259-1268.