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Residual burden of liver disease after HCV clearance in hemophilia: a word of caution in the era of gene therapy

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Key Points

- Residual risk factors of liver damage after HCV clearance are frequent.
- A specific diagnostic workup is mandatory for hemophilia gene therapy.

Ruling out advanced fibrosis/cirrhosis is mandatory for persons with hemophilia (PWH) who are candidates for gene therapy. However, clinical evaluation and noninvasive tests (NITs) may be inaccurate after hepatitis C virus (HCV) clearance. We conducted a prospective hepatological screening to detect advanced fibrosis/cirrhosis in PWH after HCV clearance. Any risk factor of chronic liver damage was registered by using biochemical data, liver stiffness measurement (LSM), and ultrasound (US). A pre/post-HCV clearance analysis was conducted prospectively in a subgroup of patients who underwent LSM, US, and NITs for fibrosis. We evaluated 119 patients (median age, 53 years; range, 36-87 years) with a previous HCV infection (hemophilia A, n = 108; hemophilia B, n = 11). Ninety-six (81%) presented at least 1 potential risk factor of chronic liver damage. Metabolic risk factors were the most prevalent, with 51 patients (44%) having US steatosis. In 21 patients (18%), clinical, biochemical, liver morphology, and/or LSM were suggestive of advanced fibrosis/cirrhosis. Furthermore, 10 patients (8%) had esophageal varices and 3 (3%) had hepatocellular carcinoma. In 57 patients included in the prospective analysis, LSM and NITs were reduced after HCV clearance ($P < .05$), but US signs specific of cirrhosis remained unchanged. Overall, 23 of 80 patients (29%) with LSM <10 KPa had at least 1 US sign suggestive of advanced fibrosis/cirrhosis. A similar proportion (18%) was observed for LSM <8 KPa. Overall, risk factors of chronic liver damage are frequent after HCV clearance, but changes in LSM and NITs after clearance may be inaccurate to rule out advanced fibrosis/cirrhosis. A specific diagnostic workup is warranted to evaluate liver health in PWH in the era of gene therapy.

Introduction

Hepatitis C virus (HCV) infection is highly prevalent among persons with hemophilia (PWH) treated in the past with plasma-derived products.[1] As a consequence, early detection and prompt management of HCV infection have been the pillar of liver health.[1,2] The introduction of direct antiviral agents (DAA) has allowed to achieve a success rate of HCV clearance as high as 80-100% and PWH are no exception.[3] Unfortunately, although a sustained virological response (SVR) abolishes the risk of liver complications

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in the early disease stages, advanced fibrosis/cirrhosis at the time of SVR may curb the reduction of such complications as portal hypertension, hepatocellular carcinoma (HCC), and the need for transplantation.[4-10] Furthermore, highly prevalent comorbidities and lifestyles, such as obesity, diabetes, and alcohol intake, are per se crucial risk factors for the progression of liver damage in PWH.[11-13]

With this background, although the achievement of SVR is the primary intervention to achieve liver health in patients who are HCV positive, selected patients require a maintenance of close hepatological surveillance.[14] Firstly, patients who at the time of SVR have compensated liver disease in the form of advanced fibrosis/cirrhosis (the so called compensated advanced chronic liver disease [cACLD]) must continue the 6-monthly screening for HCC, which remains the most frequent complication despite HCV clearance.[8,10,15] Secondly, patients who had already experienced complications because of portal hypertension (eg, varices, ascites, variceal hemorrhage, and hepatic encephalopathy) have only a partial reduction of portal pressure, which, despite HCV clearance, exposes them to a risk of decompensation/further decompensation.[4,6] Lastly, a first event of decompensation should be monitored and prevented in patients with cACLD achieving SVR when another risk factor of liver damage is present (alcohol intake and metabolic comorbidities).[14]

All the aforementioned observations are important to implement programs for liver health in the era of gene therapy in hemophilia.[16-18] Indeed, data from clinical trials of this innovative therapy have renewed the traditional alliance between hematologists and hepatologists for the management of PWH, in order to better identify the target population and avoid potential liver-related adverse effects. Accordingly, patients with advanced fibrosis/cirrhosis must be excluded from gene therapy, but the diagnostic workup to rule out this condition cannot be limited to the most common noninvasive tests (NITs), which do not always correspond to a histologically proven downstaging of liver damage after HCV clearance.[19]

Herein, we report the data of a hepatological screening program in a series of patients who were HCV positive with hemophilia who had already obtained virus clearance to evaluate liver health. The hepatological evaluation was part of the multidisciplinary program of the Joint Ultrasound Evaluation in Hemophilia (the JOINEM study approved by our institution) and was aimed at the following: (1) detecting the presence of any persistent and/or incidental risk factor of chronic liver damage after HCV clearance; (2) describing the morphological changes of the liver on ultrasound (US) imaging, the trend of liver stiffness measurement (LSM), and other NITs of fibrosis before and after anti-HCV therapy; and (3) optimizing the risk and management of liver-related complications detected at the time of screening by the means of a multidisciplinary approach. These objectives are crucial to optimize patient selection in the era of gene therapy with the liver as the target organ of coagulant-factor expression.

Patients and methods

Study cohort and data collection

This study reports data of the first 119 patients who were positive for HCV antibody, addressed to an active hepatological screening program by means of clinical, instrumental, and laboratory variables at the Angelo Bianchi Bonomi center for Hemophilia in Milan, Italy, from November 2020 to July 2022. The study was approved by the Milan Area 2 Ethics Committee (199_2021bis). The study was conducted in accordance with the Declaration of Helsinki. At inclusion, all patients were HCV-RNA negative owing to eradication by antiviral therapy or spontaneous virus clearance. Comorbidities and risk factors of chronic liver damage (eg, metabolic, alcohol, and other viral etiologies) were systematically recorded. In detail, the threshold of risk for alcohol exposure was defined by an alcohol intake >14 alcoholic units (AUs) per week, in agreement with the Italian Institute of Health guidelines on alcohol consumption.[20] A diagnosis of concomitant nonalcoholic fatty liver disease (NAFLD) was made after detection of liver steatosis at US exploration and exclusion of alcoholic liver disease.[21] Autoimmunity and/or cholestatic liver disease were evaluated if suspected after the first assessment. US exploration, LSM by Fibroscan, and FIB-4 and APRI as NITs[22] were carried out at the time of screening. The diagnosis of advanced fibrosis/cirrhosis was made according to clinical and radiological criteria (US and LSM) and histological data when necessary. The detection of liver-related complications and clinical complications or decompensation (eg, endoscopic/radiological signs of portal hypertension, HCC, ascites, bleeding because of portal hypertension, and hepatic encephalopathy) were considered suggestive of cirrhosis. Two separate hepatologists (V.L.M. and N.B.) concurred for a diagnosis of advanced fibrosis/cirrhosis, and lack of agreement was solved by a third hepatologist (A.L.F.). The surveillance of esophageal varices and the management of the risk of portal hypertension and related complications was based on the last Baveno VII consensus.[14]

In patients who had obtained HCV clearance after antiviral therapy, US, LSM, and NITs were also recorded as the last result available before virus eradication and compared with those obtained at the time of screening for a pre/post-SVR subanalysis.

Patients with de novo HCC were addressed to a tailored approach after a multidisciplinary evaluation by radiologists, oncologists, and surgeons.[23] All HCC were classified according to Milan in/out criteria for transplantation based upon the presentation as a single liver nodule <5 cm or 3 nodules <3 cm.[24] The control of the bleeding risk associated with hemophilia for any invasive procedure was planned with the hematologists and hepatologists.[25,26] All patients were evaluated for their joint status by means of the hemophilia joint health score and hemophilia early arthropathy detection with US scoring systems (supplemental Materials).

Statistical analysis

SPSS 28.0 statistical package (IBM) was used for data analysis. All results were presented as medians and minimum-maximum ranges for continuous variables and numbers and proportions for categorical variables. Comparisons among groups were made by nonparametric tests. Changes in morphological aspects of the liver, LSM, and NITs at 2 time points were evaluated before HCV clearance and at the time of hepatological screening by pair-data tests such as Wilcoxon and McNemar tests when appropriate. The statistical significance threshold was P value <.05 for all tests used in this analysis.

Table 1. Main clinical and biochemical data at the time of screening

Age at screening (y)	53 (36-87), n (%)
BMI (kg/m^2)	24.6 (17.3-40.6)
Hemophilia	
A	108 (91)
Mild/moderate/severe	19/13/76 (16/11/64)
B	11 (9)
Mild/moderate/severe	1/2/8 (1/2/7)
Years from eradication	5 (1-33)
Age at eradication or datable clearance	46 (13-81)
Alcohol (≥14 AUs per week)	14 (12)
NAFLD	46 (39)
Patients with alteration of transaminases/ cholestasis	17(14)/26(22)
Elevated AST (>33 U/L)/ALT (>41 U/L)	13 (11)/8 (7)
Elevated GGT (>36 U/L)/elevated ALP (>104 U/L)*	22 (19)/9 (8)
AST (U/L)/ALT (U/L)	25 (15-93)/24 (9-80)
GGT (U/L)/ALP (U/L)	20 (6-122)
Cholesterol (mg/dL)	178 (89-253)
HDL (mg/dL)/LDL (mg/dL)	47 (24-85)/101 (47-180)
Total bilirubin (mg/dL)	0.6 (0.2-3.6)
Cholinesterase (U/L)	7880 (3563-12232)
Total proteins (g/dL)/albumin (g/dL)	7.3 (6.3-8.10)/4.6 (3.5-5.5)
Alphafetoprotein (ng/mL)	2.3 (0.1-61.9)
Hemoglobin (g/dL)	14.1 (10-19.6)
White blood cells (units × 10^3/μL)	5.79 (2.33-11.65)
Neutrophils (%)/lymphocytes (%)	57 (22-83)
Platelets (units× 10^3/μL)	215 (67-442)
Patients with platelets ranging from 100-150×10^3/μL	7 (6)
Patients with platelets <1× 10^3/μL	5 (4)
Triglycerides (mg/dL)	96 (40-513)
Glycemia (mg/dL)	89 (67-213)
Creatinine (mg/dL)	0.96 (0.59-1.71)
Na (mmol/L)	141 (123-146)
Liver stiffness (KPa)†	5.5 (2.3-45)
APRI score/ FIB-4 score	0.35 (0.16-1.57) / 1.39 (0.43-7.02)
Ultrasound data‡	
Liver Steatosis	51 (44)
Irregular or nodular liver surface	23 (20)
Liver caudate lobe hypertrophy	8 (7)
Splenomegaly	32 (27)
Portal trunk dilated	9 (8)
Focal liver lesions	12 (10)

Continuous variables are presented as medians and minimum-maximum ranges, and categorical variables are presented as numbers and proportions.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; GGT, gamma-glutamil transferase; HDL, high density lipoprotein; LDL, low density lipoporotein.

*Data available on 97 patients.

†Data available on 90 patients.

‡Data available on 117 patients.

Results

Clinical characteristics at inclusion

One hundred and nineteen male patients (median age, 53 years; range, 36-87 years), including 108 (91%) with hemophilia A (mild, n=19; moderate, n = 13; severe, n = 76) and 11 (9%) with hemophilia B (mild, n = 1; moderate, n = 2; severe, n = 8) underwent hepatological evaluation. Their median hemophilia joint health score was 15 (range, 0-57), and median hemophilia early arthropathy detection with US was 12 (range, 0-59). All patients underwent screening for the most critical risk factors of chronic liver damage, along with biochemical tests needed for the calculation of APRI and FIB-4 to evaluate liver health. A total of 117 patients also underwent abdomen US evaluation, and 90 underwent LSM by transient elastography.

The main clinical and biochemical data at baseline presentation are detailed in Table 1. Overall, 17 (14%) of 26 patients (22%) had transaminases and/or cholestatic enzymes (eg, γ-glutamiltransferase, alcaline phospatase) above the physiological range of normality, notwithstanding HCV clearance.

At the time of screening, 12 patients (10%) had obtained spontaneous HCV clearance, whereas the remaining 107 (90%) had obtained clearance after at least 1 attempt with antivirals. In detail, 40 patients (34%) had experienced treatment failure with interferon-based therapy regimens with/without ribavirin, and 64 patients (54%) obtained SVR after DAA. The median age at the time of HCV eradication was 46 years (range, 13-81 years), and hepatological screening was conducted 5 years (range, 1-33 years) after this achievement. HCV genotypes 1a/1b were the most prevalent at the time of successful antiviral therapy (supplemental Table 1). A total of 33 patients (28%) had a history of HCV as a single viral infection, whereas 53 (45%) were HBV/HCV positive, 10 (8%) had HCV/human immunodeficiency virus, and 23 (19%) had HCV/HBV/human immunodeficiency virus . All viral infections other than HCV were controlled by antiviral therapy in agreement with the protocols of therapy.[27,28] At screening, US analysis revealed steatosis in 51 patients (44%), irregular/nodular surface in 23 (20%), caudate lobe hypertrophy in 8 (7%), portal vein enlargement in 9 (8%), and splenomegaly in 32 (27%). The median LSM value was 5.5 KPa (range, 2.3-45), and median values of APRI and FIB-4 were 0.35 (range, 0.16-1.57) and 1.39 (range, 0.43-7.02), respectively.

Risk factors of disease progression after HCV clearance

Table 2 reports data on metabolic comorbidities and alcohol habits at the time of screening. Ninety-two patients (77%) had at least 1 metabolic condition, with arterial hypertension being the most prevalent (n = 46; 39%). The burden of metabolic comorbidities was proportionally higher with aging (supplemental Table 2). A total of 85 patients (71%) were maintaining alcohol abstinence at the time of screening. However, the intake, expressed in AUs per week, was 0 to 6, 7 to 14, and ≥14 AUs per week in 89 (75%), 16 (13%), and 14(12%) patients, respectively. On the whole, up to 96 patients (81%) in the present cohort had at least 1 potential risk factor of chronic liver damage on top of their previous history of HCV infection. Nonalcoholic fatty liver disease (NAFLD) or

Table 2. Risk factors of disease progression detected at the time of screening

Alcohol consumption	n (%)
AU intake per week	2 (0-35)
Patient distribution per AU intake per week	
0-6	85 (71)
7-14	16 (13)
≥14	14 (12)
Metabolic	
Type 2 diabetes	8 (6)
Arterial hypertension	46 (39)
Dyslipidemia (triglycerides > 150 mg/dL, HDL< 40 mg/dL or need of lipid lowering drugs)	51 (43)
Overweight (BMI 25-30 kg/m^2)	45 (38)
Obesity (BMI ≥30 kg/m^2)	10 (8)
Combined risk factors	
At least 1 potential metabolic risk factor for liver disease	92 (77)
Three or more metabolic risk factors with alcohol intake less than 14 units per week	25 (21)
At least 1 potential risk factor for liver disease (metabolic or alcohol)	96 (81)

BMI, body mass index.

Table 3. Liver morphology (US exploration) and LSM before and after SVR

Parameter	Pre-SVR, n (%)	Post-SVR, n (%)	*P* value
Irregular/nodular surface	13 (23)	12 (21)	1.000
Liver caudate lobe hypertrophy	5 (9)	2 (4)	.375
Splenomegaly	20 (35)	18 (32)	.687
Portal vein trunk dilated	15 (26)	5 (9)	.006
At least 1 US sign of cirrhosis	27 (47)	22 (39)	.180
LSM (kPa)	8.3 (3.6-45.7)	5.6 (2.3-45)	<.001
Patients with LSM <8 kPa (%)	28 (49)	39 (68)	.003
Patients with LSM <10 kPa (%)	34 (60)	49 (86)	<.001

alcoholic liver disease were suspected in 46 (39%) and 14 (12%) patients, respectively.

Liver morphology at US exploration, LSM, and NITs before and after SVR

A total of 57 of 119 patients (48%) had a record of liver US exploration, LSM, and NITs (eg, APRI and FIB-4) both before SVR and at the time of screening (median time difference, 5 years [range, 1-16]) and were thus included in the pre/post-SVR analysis (Table 3) (Figure 1).

The proportion of patients with morphological signs suggestive of cirrhosis did not change before and after SVR for all the most relevant data, with the single exception of portal vein trunk dilation, detectable in 15 patients (26%) before and in 5 (9%) after SVR ($P = .006$).

Pre-SVR LSM was 8.3 KPa (range, 3.6-45.7), which is significantly higher than post-SVR LSM (5.6 kPa; range, 2.3-45.0 kPa) ($P < .001$). Accordingly, the number of cases with LSM <8 KPa was 28 (49%) before SVR vs 39 (68%) after SVR ($P = .003$). Similarly, the number of patients with LSM <10 KPa was 34 (60%) before SVR vs 49 (86%) after SVR ($P < .001$), confirming that HCV clearance reduced the LSM independently of the cutoff used as the basis of the most validated threshold of LSM used to rule out advanced fibrosis/cirrhosis.[22] Similar changes were observed for APRI and FIB-4.

Liver-related complications, interventions, and decisions on the hepatological follow-up schedule

In the whole cohort, the number of patients for each liver-related complication detected after the screening were as follows: 10 (4%) with history of esophageal varices, 4 (3%) with history of previous decompensation (2 ascites and 3 variceal bleeding), 9 (8%) with undefined/nonmalignant focal liver lesions, and 3 (3%) with HCCs (2 of them were outside Milan criteria for the transplantation).[15] One of the HCCs occurred in a noncirrhotic liver and histology revealed parenchymal steatohepatitis around the tumor, likely because of metabolic factors (eg, diabetes and arterial hypertension). Clinical details for each patient with HCC are provided in supplemental Table 3.

Consistent with the aforementioned complications, 5 patients with varices started therapy with carvedilol to prevent decompensation or further decompensation,[14,29] and 5 patients were addressed to a new endoscopic control before deciding to start bleeding prophylaxis because of portal hypertension. All 9 patients with undefined/nonmalignant focal liver lesions were addressed to a 3-monthly imaging follow-up with contrast-enhanced computer tomography or magnetic resonance. All 3 patients with HCC underwent transplantation. Radiofrequency, resection, chemoembolization, and/or systemic chemotherapy (eg, atezolizumab/bevacizumab) were chosen and/or combined on the basis of a case-by-case decision (supplemental Table 3). Specifically, downstaging was achieved before transplantation for the 2 patients with HCC who were outside the Milan criteria. After transplantation, a patient had extrahepatic HCC recurrence and was on an oral tyrosine-kinase inhibitor and best-supportive therapy. The others were on close hepatological follow-up without significant complications after transplantation.

Finally, by considering the combined screening on potential residual risk factors of chronic liver damage, liver morphology, LSM, and NITs, 3 patients (2%) were recommended to be discharged. Furthermore, 95 patients (80%), despite not showing advanced fibrosis/cirrhosis, were addressed to annual follow-up because of the persistence of risk factors of chronic hepatitis. The remaining 21 patients (18%) have been considered to have advanced fibrosis/cirrhosis and were therefore addressed to a 6-monthly or shorter hepatological follow-up.

Table 4 combines several levels of LSM at the time of screening and shows the most important variables conditioning the final decision on the presence or absence of advanced fibrosis/cirrhosis. Even for the categories at low risk, as defined by LSM <10 KPa or below the more restricted threshold of 8 KPa (supplemental Table 4), there were US morphological data of the liver and/or complications that suggested the presence of advanced chronic liver disease despite HCV clearance.

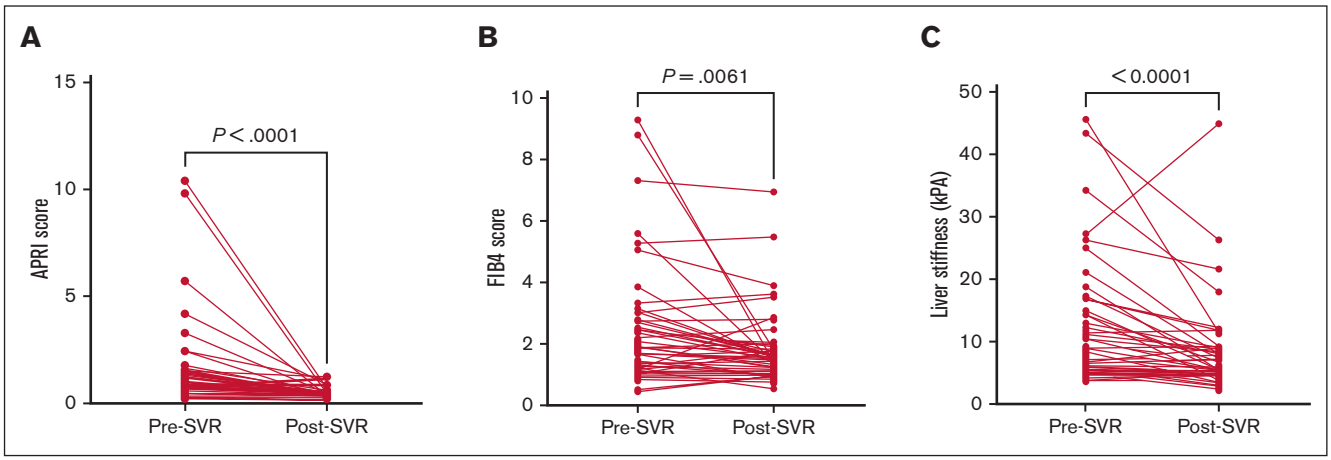

Figure 1. All non-invasive tests of fibrosis declined after HCV clearance. APRI (A), FIB4 (B) scores and liver stiffness (C) variation pre-SVR and post-SVR at screening.

Discussion

This study reports data from a hepatological screening program of patients with HCV infection with hemophilia who had obtained eradication of the virus after antiviral therapy or spontaneous clearance. We found that up to 81% of the patients had at least 1 risk factor of chronic liver damage on top of a previous history of HCV infection, and NAFLD or alcoholic liver disease was found in 39% and 12% of the cohort, respectively. In a pre/post-SVR prospective subgroup analysis, despite the consistent reduction of LSM and NITs as marker of fibrosis, up to 39% of cases had at least 1 morphological sign suggestive of advanced fibrosis/cirrhosis (eg, irregular/nodular surface of the liver, liver caudate lobe hypertrophy, dilation of the portal trunk, and splenomegaly) that, together with residual risk factors of liver damage, demands specialized follow-up despite HCV clearance. Furthermore, because of the hepatological evaluation, 18% of patients were addressed to 6-monthly HCC screening and 14% needed a specialized intervention because of detection of HCC or undefined/nonmalignant focal liver lesions or a need to prevent the complications associated with portal hypertension. These data clearly demonstrate that even after SVR a large proportion of PWH should attend a regular hepatological follow-up. The persistence of risk factors of liver damage or the suspicion of a residual advanced fibrosis/cirrhosis at the time of the hepatological screening were the main reasons for addressing patients to this follow-up.

We found a high prevalence of metabolic comorbidities, which are known risk factors for steatosis/steatohepatitis. Indeed, 77% of patients had at least 1 metabolic disease and 39% had a NAFLD diagnosis.[21] Notably, the latter condition was also detectable in patients with no increase of liver enzymes (34% in this series), confirming that NAFLD can be suspected by means of an accurate anamnesis and diagnosed by US even in cases with normal liver enzymes. The high prevalence of a metabolic disease of the liver detected in our cohort is in line with the epidemiological data from the European Association for the Study of the Liver (EASL) HEPAHEALTH Steering Committee (report 2018), which accounted

Table 4. Data on post-SVR liver stiffness measurement (LSM) matched with the most important clinical and US features suggestive of advanced fibrosis/cirrhosis

	Post-SVR LSM categories (kPa)			
	<10 (n = 80), n (%)	10-15 (n = 4), n (%)	≥15 (n = 6), n (%)	*P* (linear trend)
At least 1 US sign suggestive of cirrhosis	23 (29)	4 (100)	5 (83)	<0.001
Irregular or nodular liver surface	9 (11)	3 (75)	5 (83)	<0.001
Liver caudate lobe hypertrophy	4 (5)	1 (25)	1 (17)	0.124
Splenomegaly	17 (22)	3 (75)	5 (83)	<0.001
Portal vein dilatation	4 (5)	1 (25)	1 (17)	0.124
History of previous decompensation	1 (1)	1 (25)	2 (33)	<0.001
History of esophageal varices	2 (3)	3 (75)	3 (50)	0.045
NAFLD	29 (36)	1 (25)	0	0.068
Alcohol consumption (7-14 AU per week)	9 (11)	0	1 (17)	0.889
Alcohol consumption (>14 AU per week)	10 (13)	1 (25)	1 (17)	0.613
At least 1 metabolic risk factor	58 (73)	3 (75)	6 (100)	<0.001
Platelet count $<1.5 \times 10^5$ /μL	6 (8)	1 (25)	3 (50)	0.223
Platelet count $<1.1 \times 10^5$ /μL	1 (1)	1 (25)	2 (33)	<0.001

NAFLD as the leading cause of liver transplantation in western countries.[30,31] In PWH, the prevalence of overweight/obesity is higher than in the past,[18,32] because the arthropathy typically associated with the inherited bleeding disorder exposes them to a higher risk of sedentary life and thus overweight.[11,33] Accordingly, 38% and 8% of patients in our series were overweight and obese, respectively, which increases the risk of diabetes, dyslipidemia, arterial hypertension, and, ultimately, NAFLD, which is the liver expression of the metabolic syndrome.[33,34] We also found that, although the vast majority had a minimal to moderate alcohol intake, 12% of the whole cohort were heavy drinkers (≥14 AUs per week), which is a risk factor for such systemic complications as chronic hepatitis/cirrhosis.[31,35]

We also carried out a prospective pre/post analysis of liver changes as explored by US, LSM, and NITs by evaluating 2 time points at screening and at virus eradication. In this subanalysis, we found that SVR reduced over time all the noninvasive markers of fibrosis. In particular, the proportion of patients with a LSM <10 KPa, the threshold commonly used to rule out cACLD/compensated cirrhosis,[14,36] increased from 60% to 86%, with a similar trend for all NITs. However, the proportion of patients with morphological signs of advanced fibrosis/cirrhosis at US exploration did not change between the 2 time points for all the features, except for portal vein dilatation. Lack of a liver biopsy did not allow us to evaluate which was the most accurate noninvasive strategy to rule out an advanced stage of fibrosis/cirrhosis.

In this cohort, 3 patients with HCCs (3%) were found. This is not unexpected, because the risk of HCC persists despite HCV clearance, and international guidelines recommend continuing 6-monthly screening in patients with SVR and advanced fibrosis/cirrhosis.[15] One of the 3 HCCs diagnosed after the screening was in a noncirrhotic liver, as demonstrated by the histology around the tumor after liver resection. This patient had diabetes and arterial hypertension, confirming that cases exposed to metabolic risk factors of chronic liver damage should be periodically evaluated for the risk of HCC. Although the therapeutic strategies of HCC have made enormous progress, early detection of this cancer still remains the most efficacious tool to ameliorate survival.[15] We also found that 9 patients (8%) had undefined/nonmalignant hepatic liver lesions needing strict imaging follow-up. Real life data after successful therapy with DAA demonstrated that, in line with patients with a previous history of HCC, those with undefined/nonmalignant hepatic liver lesions may be at high risk of HCC development.[37] Thus, we recommend a periodical hepatological evaluation in PWH, as also suggested by Isfordink et al who found that in a cohort of 199 patients with SVR after interferon-based regimens or DAA there was a 21% prevalence of advanced fibrosis and 42% of cirrhosis, as well as 4 patients with HCC.[38]

The diagnosis of advanced chronic liver disease is essential to allocate patients to the most appropriate schedule of visits for liver health. Firstly, these patients would benefit from a 6-monthly screening for HCC, because early detection warrants curative treatments. Secondly, an adequate stratification of the risk of complications related to portal hypertension is mandatory, because chronic therapy with traditional nonselective beta-blockers/carvedilol and/or repeated sessions of endoscopic band ligation may be needed.[14] Liver biopsy is still considered the reference standard to unmask the presence of advanced fibrosis/cirrhosis when a patient falls in the diagnostic gray zone. A few small-sized studies compared LSM and NITs with liver biopsies after HCV eradication,[19,39] but the rate of misclassification of advanced fibrosis/cirrhosis was around 60%. Accordingly, guidelines from the EASL discourage the routine use of LSM or NITs to detect fibrosis regression after SVR, because these tests are not accurate enough.[22] In this cohort, morphological changes of the liver at US exploration, such as irregular/nodular liver surface and the caudate liver lobe hypertrophy, did not significantly change before and after SVR. Notably, these morphological aspects have 80% to 100% specificity for cirrhosis.[40] However, this high degree of accuracy to rule-in advanced fibrosis/cirrhosis has never been tested after HCV eradication. Therefore, further investigation is needed to demonstrate whether these morphological aspects capture the persistence of advanced fibrosis/cirrhosis better than LSM and/or NITs after successful antiviral therapy. It is our opinion that patients classified as having advanced fibrosis/cirrhosis by a comprehensive evaluation of a pre-SVR history of noninvasive assessments (LSM and NITs) together with liver complications and liver morphology should carry on a 6-monthly hepatological evaluation to control the risk of HCC and portal hypertension. We also believe that this cautious approach is utmost indicated if a risk factor of chronic liver damage is present. In agreement with international clinical recommendations, liver biopsy should be considered only if histology is needed for the clinical decision process.[22] This could be the case for PWH who are candidates to gene therapy, because the detection of advanced fibrosis/cirrhosis is crucial to prevent potential liver-related risks of this approach. However, the decision for this invasive test should be taken in highly motivated patients and case by case.[16,17,41]

Our study has limitations. Although the screening was conducted prospectively, the collection of clinical and instrumental data before SVR was retrospective. This reduced the possibility of extending the pre/post-SVR analysis to the whole cohort. Furthermore, the diagnosis of advanced fibrosis stage/cirrhosis was based on clinical history, US, LSM, and NITs, with a significant risk of overdiagnosis. Nevertheless, this kind of misclassification was acceptable to reduce the risk of severe liver complications, particularly in patients presenting with clinical and instrumental features suggesting advanced fibrosis/cirrhosis before SVR or in those still exposed to potential risk factors of chronic liver damage such as alcohol and/or metabolic factors. At the same time, the high prevalence of advanced stages of HCC may be, at least in part, influenced by the 2 years of pandemic, which discouraged patients to attend a regular schedule of visits. Finally, the hepatological screening program is still ongoing, therefore, that we cannot exclude a selection bias justifying the prevalence of advanced chronic liver disease in the cohort reported here. However, real life data on the incidence of liver-related complications after SVR in HCV patients without hemophilia are in line with the risk observed in this study.[7]

In conclusion, liver health is integral to the multidisciplinary care of PWH, particularly in the era of gene therapy with 2 novel adeno-associated viral vector therapies approved for hemophilia A and B that are targeting the liver. This study demonstrates that even after successful antiviral therapy, PWH still need hepatological evaluation because of the high proportion of cases with residual risk factors of chronic liver damage and the complications associated with advanced stages of the disease. LSM and NITs indeed

improve after SVR, but these may be inaccurate to rule out advanced fibrosis/cirrhosis. A specific diagnostic workup led by hepatologists together with hematologists is thus warranted to maintain liver health in PWH. This will also be useful to make the best stratification for patients who might benefit from gene therapy without significant risks for liver health.

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Authorship

Contribution: F.P. and V.L.M. were responsible for conceptualization; N.B. and V.L.M. curated the data; N.B. and V.L.M. reported formal analysis; F.P. acquired funding; N.B., C. Capelli, C. Caputo, S.S., S.A., A.C., R.G., A.L.F., and A.S. were responsible for investigation; V.L.M., N.B., and F.P. provided methodology; V.L.M. and F.P. supervised the study; V.L.M. and N.B. wrote the original draft; and F.P., A.L.F., and A.S. wrote, reviewed, and edited the manuscript.

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