Cirrhosis, High Age and High Body Mass Index Are Risk Factors for Persisting Advanced Fibrosis After Sustained Virological Response in Chronic Hepatitis C

M. Hedenstierna; A. Nangarhari; A. El-Sabini; O. Weiland; S. Aleman

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Abstract and Introduction

Abstract

We aimed to assess fibrosis with liver stiffness measurement long–term after sustained virological response of chronic hepatitis C and to identify risk factors associated with persisting fibrosis. In this cross–sectional study, patients with chronic hepatitis C and pretreatment advanced fibrosis or cirrhosis treated successfully at Karolinska University Hospital with an interferon–containing regimen underwent liver stiffness measurement with FibroScan. The impact of potential risk factors for persisting fibrosis was estimated. We included 269 patients with a median follow–up time of 7.7 years (range 0–20), 84 with a follow–up time of ≥10 years. Patients with pretreatment cirrhosis had a significantly higher median liver stiffness level (8.5 kPa 95% CI 7–9.1) at follow–up, than patients with advanced fibrosis (6 kPa 95% CI 5.5–6.4). A majority improved their fibrosis stage after sustained virological response, but 24% had persisting advanced fibrosis with a liver stiffness level of ≥ 9.5 kPa. Among patients with pretreatment cirrhosis, the proportion with persisting advanced fibrosis diminished with longer follow–up time, from 48% after <5 years to 21% after >10 years. The main risk factors for persisting advanced fibrosis were pretreatment cirrhosis, high age and body mass index. In conclusion, fibrosis improves substantially during long–term follow–up after sustained virological response in hepatitis C patients with pretreatment advanced liver fibrosis. Lifestyle intervention to decrease weight in obese persons and treatment before establishment of cirrhosis should therefore be recommended to avoid persistence of advanced fibrosis after virological cure.

Introduction

Infection with hepatitis C virus (HCV) is a global health problem with an estimated 70 million chronically infected people and 750 000 deaths every year from HCV–related causes.[1,2] The risk for HCV–related morbidity and mortality increases with the stage of liver fibrosis, and patients with compensated cirrhosis have an annual risk of 7% to develop decompensated liver disease or hepatocellular carcinoma (HCC).[3] Current guidelines therefore recommend surveillance for HCC with ultrasound every 6 months for patients with HCV–related advanced liver fibrosis or cirrhosis.[4] Because of this, accurate measurement of hepatic fibrosis is important for the clinical management of patients with chronic HCV infection.

The gold standard for staging liver fibrosis is by liver biopsy. A liver biopsy provides information on the stage of liver fibrosis, but also on the necroinflammatory activity in the liver.[5] In recent years, liver stiffness measurement (LSM) by transient elastography has replaced liver biopsy in clinical practice in many countries. This noninvasive method measures the liver stiffness by ultrasound and yields a composite result of both liver fibrosis and inflammation.[6] LSM is accurate for the diagnosis of significant fibrosis and cirrhosis in patients with chronic hepatitis C and correlates to the degree of portal hypertension and the risk to develop HCC.[7–9] LSM is less validated in patients with sustained virological response (SVR) after HCV treatment, and there are no established LSM cut–offs for fibrosis stages after achieved SVR.[10] The risk to develop HCC and other liver–related complications decreases after SVR, but does not disappear.[4,11,12] Pretreatment cirrhosis and persisting cirrhosis after achieved SVR has been associated with a high post–treatment risk for liver–related complications and HCC.[13–16] Recent studies have investigated the association of LSM levels at SVR with the risk to develop HCC, but with contradicting results.[17,18]

Several studies with paired liver biopsies have shown that liver fibrosis and cirrhosis will improve after achieved SVR in a majority of patients, but also that, in 1%–14% of patients, fibrosis will progress.[19–21] Most studies on fibrosis regression after SVR have short follow–up times, and the long–term effect of achieved SVR on liver fibrosis is less well studied. We also lack knowledge on the long–term effect of comorbidities and other risk factors on liver fibrosis after achieved SVR.

The aim of this study was to investigate the long–term effect of achieved SVR on liver fibrosis, measured as liver stiffness with transient elastography, in a cohort with pretreatment advanced chronic HCV infection. We also aimed to identify risk factors associated with persisting fibrosis.

Patients and Methods

Patients and Study Design

In this cross–sectional study, we included patients with pretreatment METAVIR F3 fibrosis or cirrhosis (F4), who had achieved

SVR after HCV treatment at Karolinska University Hospital, Sweden, between 1992 and 2013. Patients with a liver transplantation or diagnosis of HCC prior to inclusion were excluded. We also excluded patients with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) coinfection.

Patients already followed up for HCC surveillance at the clinic were included in the study at their routine visits. However, many patients had been treated before HCC surveillance was an established practice or had been lost to follow–up for other reasons. These patients were identified from treatment records and were contacted and offered a follow–up visit and continued surveillance as appropriate according to current guidelines. Patients were included in the study between November 2008 and October 2016.

Sustained virological response was defined as a negative HCV RNA 6 months after the end of treatment, and follow–up time was calculated from this time–point. The pretreatment fibrosis stage was determined by the highest result of a pretreatment liver biopsy according to the METAVIR staging system or by a LSM with a median level of ≥9.5 kPa and ≥12.5 kPa corresponding to a METAVIR fibrosis stage of F3 and F4, respectively.[5,7] A clinical diagnosis of cirrhosis was also accepted. The date of the fibrosis stage defining measurement was considered the baseline date of the study, and we used baseline data on biochemistry, body mass index (BMI), alcohol abuse and diabetes mellitus from patient records within 6 months of this date.

At the clinical follow–up visit, we performed a liver stiffness measurement with FibroScan, calculated a BMI and tested for HCV RNA. A medical history was taken including questions on comorbidities and average alcohol consumption (grams per week over the last year). Only one clinical follow–up visit with LSM was included for each patient. For patients with multiple LSMs after achieved SVR, we included the most recent one.

The study was approved by the Regional Ethics Committee according to the guidelines of the Helsinki Declaration.

Measurement of Liver Stiffness

Liver stiffness was measured by transient elastography with FibroScan using the M and XL probes as appropriate. Only examinations with ten valid measurements, an interquartile range less than 30% of the median result and a success rate of at least 60% were included. The result was expressed as median LSM levels in kilopascals (kPa). As there are no established LSM cut–offs for post–SVR fibrosis stages, we used standard pretreatment cut–offs for corresponding METAVIR fibrosis stages: F0–1: <7 kPa, F2: 7.0–9.4 kPa, F3: 9.5–12.4 kPa and F4: >12.5 kPa.[5,7] Advanced fibrosis was defined as a median LSM level ≥ 9.5 kPa in this study.

Statistical Analysis

Continuous variables are presented as medians (range) and categorical variables as frequencies (percentages). The Mann–Whitney test was used for comparison of medians and the Fischer exact test for comparison of proportions. Univariate and multivariate logistic regression was used to estimate odds ratios (ORs) for persisting advanced fibrosis, defined as a liver stiffness value ≥ 9.5 kPa at follow–up. The risk factors included were gender, pretreatment fibrosis stage, age at SVR, alcohol consumption (grams per week), BMI and the presence of diabetes mellitus at follow–up.

The fibrosis stage at follow–up was correlated to follow–up time after SVR. We used the Kruskal–Wallis rank test for equality of populations. All tests were two–sided, and a *P* –value of <.05 was considered significant. Only complete data sets were analysed, and all statistical analyses were performed with Stata version 13.1 (StataCorp, TX, USA).

Results

Study Population

We identified 402 patients with pretreatment fibrosis stage F3 or F4 and SVR in our treatment records and research databases. Of these, 36 had died, developed HCC or undergone liver transplantation after SVR had been achieved, and they were therefore excluded. Of the 366 remaining patients, 284 accepted to participate in the study, and 269 of these were successfully examined with reliable LSM at a follow–up (Figure 1). Pretreatment fibrosis stage was determined by liver biopsy in 181 patients, by LSM in 81 patients and by a clinical diagnosis of cirrhosis in 7 patients. Of the 269 patients included in the study, 119 (44%) had pretreatment cirrhosis and 158 (59%) were male. Median age at SVR was 53 years (range 18–74). The median follow–up time was 7.7 years, but varied substantially due to the cross–sectional design of the study (range 0–20 years). Follow–up time was <5 years for 115 patients, 5–10 years for 70 patients and >10 years for 84 patients (). All patients included in this study had been treated with interferon–containing regimens.

Table 1. Baseline characteristics of all study patients categorized according to follow–up time <5 , 5–10 and >10 y after sustained virological response

	All	<5 y	5–10 y	>10 y
Nr of patients	269	115	70	84
Cirrhosis (%)	119 (44)	63 (55)	22 (31)	34 (40)
Age at SVR, median (range) y	53 (18–74)	56 (25–74)	53 (29–70)	50 (18–67)

Male sex, n (%)	158 (59)	71 (62)	37 (54)	50 (58)
HCV genotype 3[a] (%)	71 (29)	32 (28)	24 (39)	15 (22)
Platelets, 10^9/L, median (range)[b]	200 (60–418)	188 (60–360)	212 (79–418)	202 (89–409)
Serum albumin, median (range) g/dL[c]	39 (29–52)	39 (30–52)	41 (29–48)	39 (34–48)
APRI score, median (range)[d]	0.74 (0.22–10.5)	0.70 (0.22–9.2)	0.68 (0.24–7.4)	0.93 (0.22–10.5)
BMI, median (range)kg/m^2[e]	25 (18–40)	25.1 (17.9–40.0)	26.0 (19.0–39.0)	25.9 (19.3–39.5)
Diabetes mellitus, n (%)	28 (10)	16 (14)	5 (7)	7 (8)
History of alcohol abuse, n (%)	88 (33)	37 (32)	21 (31)	30 (35)

Y, years; LSM, liver stiffness measurement; SVR, sustained virological response; HCV, hepatitis C virus; BMI, body mass index. Number of available data: a, n = 244; b, n = 264; c, n = 221; d, n = 259; e, n = 174.

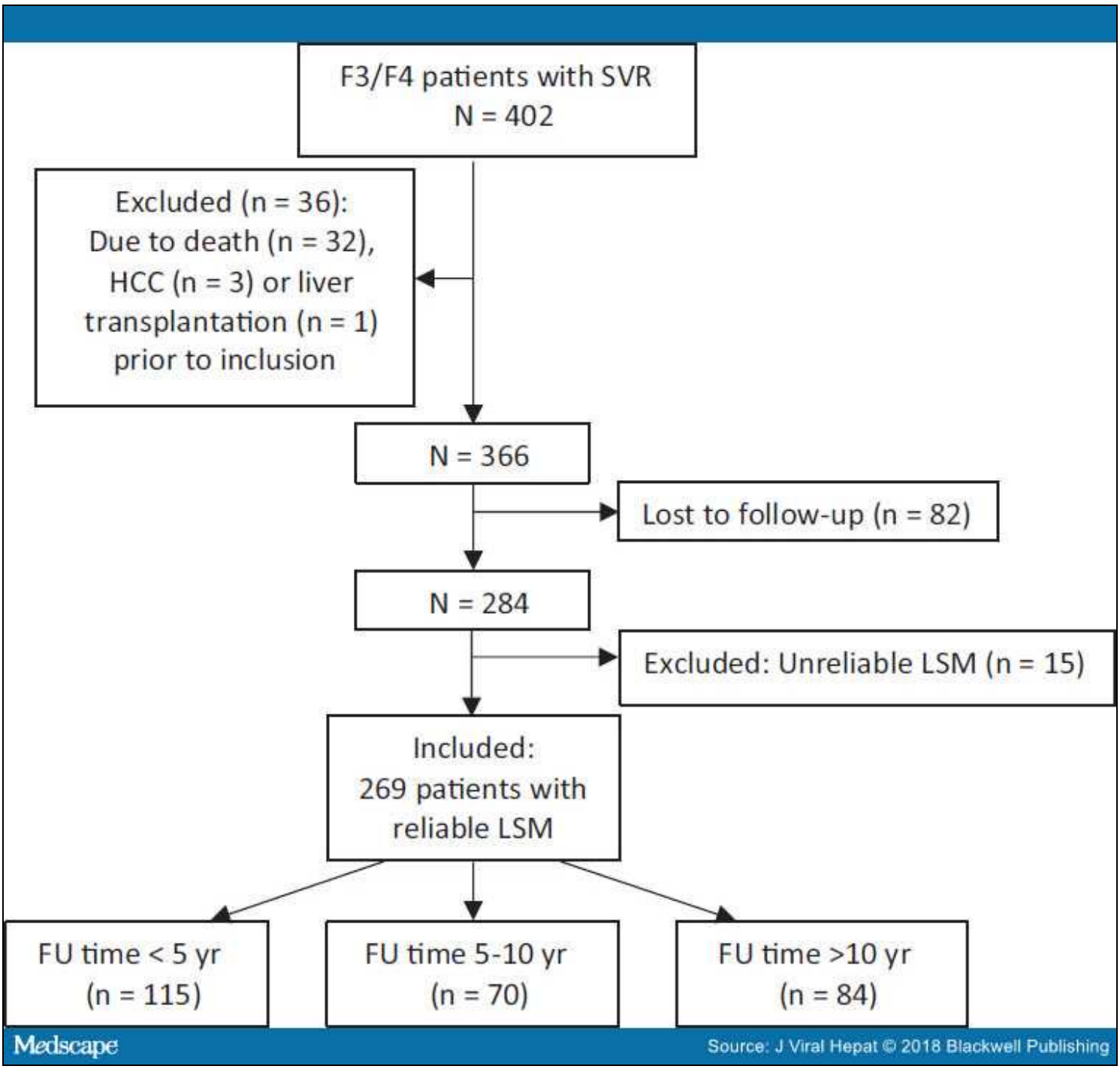

Figure 1.

Flow chart for inclusion of patients. Abbreviations: SVR, sustained virological response; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; FU, follow–up

The study population differed from the patients excluded or lost to follow–up in some respects. Patients not included in the study were to a higher degree male (73% vs 59%) and had higher baseline BMI (median 27 vs 25 kg/m^2. The remaining baseline factors, including the proportion with cirrhosis, baseline diabetes mellitus and alcohol abuse, were not significantly different for the two groups.

A history of alcohol abuse was common at baseline (33%), but at follow–up the median reported alcohol consumption was low (18 g/wk), and 110 patients (42%) reported no alcohol consumption during the last year. A minority of patients reported higher alcohol consumption, with 44 patients (17%) and 17 patients (6%) reporting more than 100 or 210 g/wk, respectively. Median BMI at follow–up was 26 kg/m^2 (range 17–43), and 45 patients (17%) had a BMI over 30 kg/m^2 at the follow–up visit. Diabetes mellitus (DM) had been diagnosed in 35 patients (13%) at follow–up, and seven of these had developed DM after SVR had been achieved.

Fibrosis Improvement After Sustained Virological Response

Median liver stiffness at follow–up was 6.6 kPa (range 2–57 kPa) compared to 13.9 kPa at baseline (range 9.5–74). However, only 81 patients were examined with LSM before treatment, and all of these had a follow–up time of less than 5 years. For patients with longer follow–up time, we only had data on pretreatment METAVIR fibrosis stage. Patients with pretreatment cirrhosis (F4) had significantly higher median liver stiffness at follow–up (8.5 kPa 95% CI 7–9.1) than patients with pretreatment fibrosis stage F3 (6 kPa 95% CI 5.5–6.4). Patients with pretreatment cirrhosis determined by liver biopsy had lower median liver stiffness at follow–up than patients with cirrhosis determined by LSM (7.4 kPa 95% CI 6–8.8 vs 9.4 kPa 95% CI 7.8–11), but this difference was not significant (*P* = .07). A scatter plot of all individual LSMs by follow–up time and baseline fibrosis stage is presented in Figure 2.

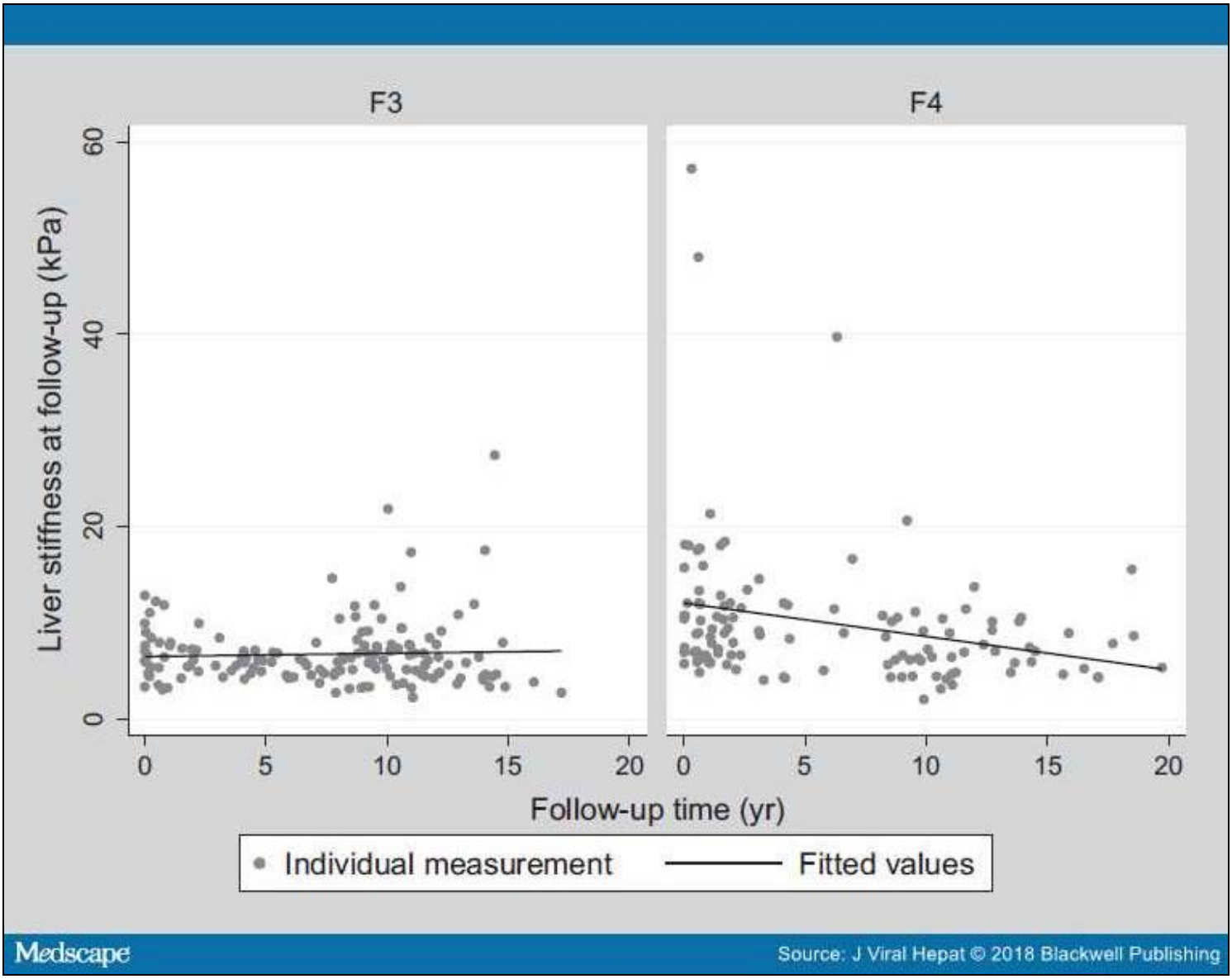

Figure 2.

The distribution of liver stiffness levels at follow–up by baseline fibrosis stage and follow–up time. Regression line over fitted values is shown

A majority (87%) of patients with fibrosis stage F3 at baseline had a liver stiffness below 9.5 kPa at follow–up, and 83% of patients with pretreatment cirrhosis had a liver stiffness below 12.5 kPa, indicating an improved fibrosis stage after achieved SVR. However, 17% of patients with cirrhosis and 13% of patients with fibrosis stage F3 did not improve their fibrosis stage, and 5% had progressed to a more advanced stage at follow–up (Figure 3).

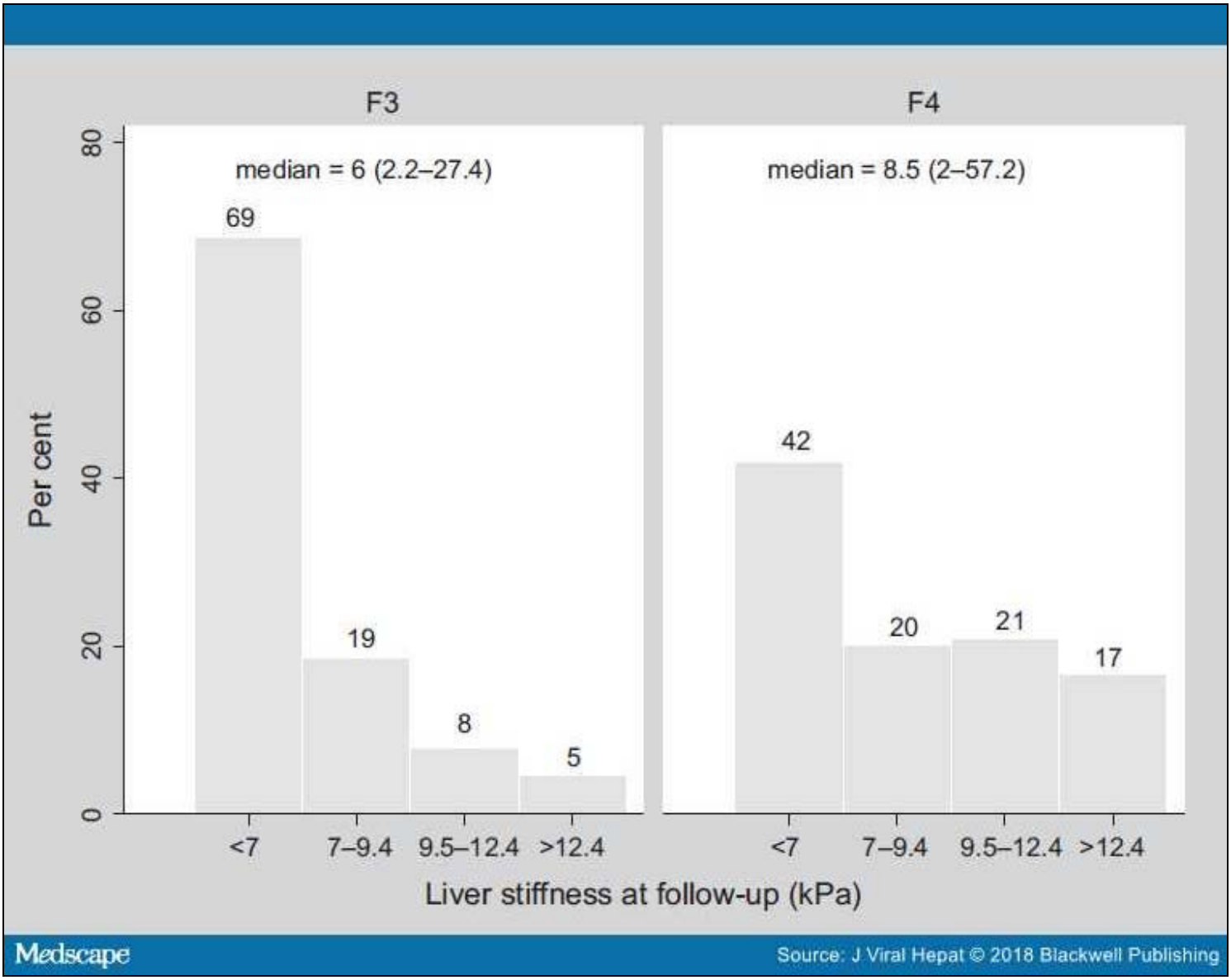

Figure 3.

The distribution of liver fibrosis stages at follow–up by fibrosis stage at baseline. Categories are based on pretreatment cut–offs for METAVIR fibrosis stages

The distribution of liver stiffness values remained similar irrespective of follow–up time for patients with pretreatment fibrosis stage F3. Significant improvement with diminishing liver stiffness with longer follow–up time was, however, seen in patients with pretreatment cirrhosis (Figure 4). For patients with pretreatment cirrhosis, the proportion with a LSM > 9.5 kPa at follow–up thus diminished from 48% for patients with <5 years of follow–up to 36% for patients with 5–10 years of follow–up, and 21% when follow–up time was >10 years (P = .02). In the small subset of patients with follow–up >15 years (n = 11), the median LSM at follow–up was 5.2 (2.7–15.5) kPa and only 9% had a LSM > 9.5 kPa, indicating persisting advanced fibrosis.

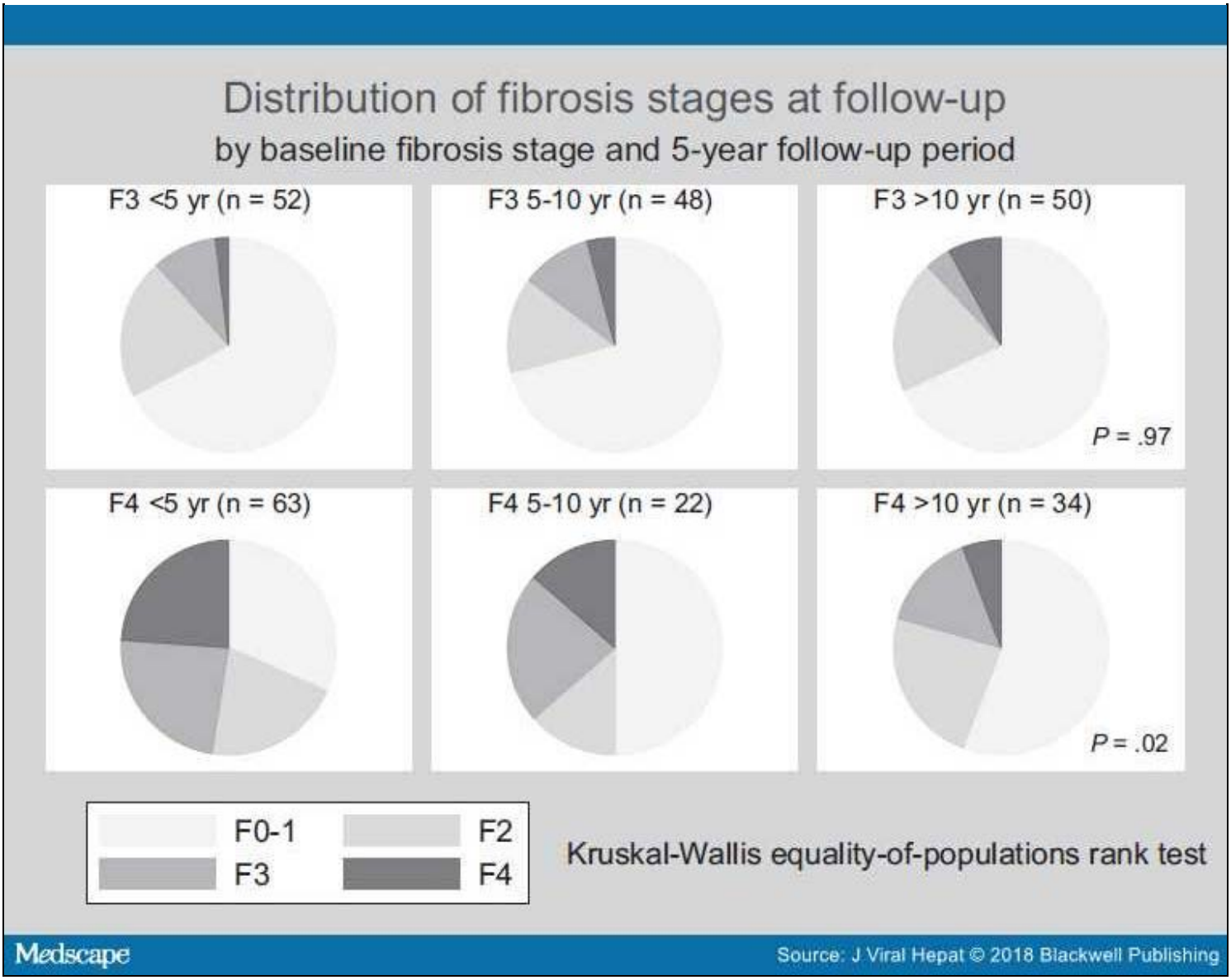

Figure 4.

The distribution of liver fibrosis stages at follow–up by fibrosis stage at baseline and 5–y follow–up period. Categories are based on pretreatment cut–offs for METAVIR fibrosis stages. The Kruskal–Wallis rank test is used to test equality of populations

Risk Factors Associated With Persisting Advanced Fibrosis at Follow–up

Overall, 64 of the included patients (24%) had mean LSM levels of ≥9.5 kPa at follow–up, indicating persisting advanced fibrosis. Of these, 19 patients had pretreatment fibrosis stage F3, and 45 patients had pretreatment cirrhosis (F4). Among those with LSM levels ≥ 12.5 kPa at follow–up (n = 27), seven patients had pretreatment F3 fibrosis, and 20 had pretreatment cirrhosis (F4). Median APRI score at follow–up was 0.38 (range 0.19–3.21) for patients with LSM values ≥ 9.5 kPa, and 0.26 (range 0.07–1.01) for patients with LSM values < 9.5 kPa. This difference was significant ($P < .001$), but the median for both groups was below standard cut–offs used to predict cirrhosis. None of the patients with a LSM below 9.5 kPa at follow–up had an APRI score indicating cirrhosis (≥1.5).

We estimated the risk for persisting advanced fibrosis (defined as ≥9.5 kPa) at follow–up, by calculating odds ratios with logistic regression for patients with different risk factors. Age, alcohol use and BMI were tested both as continuous and dichotomized variables with similar significance levels. Results are presented for the dichotomized variables to make the ORs easier to interpret ().

Table 2. Risk factors associated with a liver stiffness of ≥9.5 kPa at follow–up in patients with sustained virological response after hepatitis C treatment

	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*

Male sex	1.6	0.9–2.9	.12			
Age ≥ 55 y at SVR	2.6	1.5–4.7	.001	2.3	1.2–4.3	.008
Cirrhosis at baseline	4.2	2.3–7.7	<.001	3.9	2.0–7.2	<.001
BMI ≥ 25 kg/m^2 at follow–up	2.6	1.3–5.0	.004	2.3	1.1–4.6	.02
Diabetes mellitus at follow–up	2.8	1.4–6.0	.006	1.5	0.7–3.5	.32
Alcohol use ≥ 100 g/wk	0.6	0.3–1.4	.23			

OR, odds ratio; CI, confidence interval; SVR, sustained virological response; BMI, body mass index.

In the univariate analysis, pretreatment cirrhosis, age at SVR, BMI and diabetes mellitus at follow–up were significantly associated with a follow–up liver stiffness of ≥9.5 kPa. Alcohol use was not found to be associated with LSM levels ≥ 9.5 kPa at follow–up. However, median alcohol consumption was only 18 g/wk in this study, and 42% of the included patients did not use alcohol at all. Consequently, the influence of alcohol use on liver stiffness was difficult to evaluate in this study.

In the multivariate analysis, pretreatment cirrhosis, age ≥ 55 years at SVR and BMI ≥ 25 kg/m^2 at follow–up remained risk factors indicating persisting advanced fibrosis with ORs of 3.9 (95% CI 2.0–7.2), 2.3 (95% CI 1.2–4.3) and 2.3 (95% CI 1.1–4.6), respectively.

No significant interaction was found between risk factors and follow–up time after SVR, suggesting that the different risk factors had the same impact on liver stiffness regardless of follow–up time. Because of this, no separate analysis was performed for the different 5–year follow–up periods.

A small subset of patients with pretreatment F3 fibrosis (n = 7) had a LSM level of ≥12.5 kPa at follow–up, indicating progression to cirrhosis after successful treatment. These seven patients were much more likely to have diabetes (3/7 compared to 7/141, *P* = .002) than F3 patients that did not progress to cirrhosis after SVR. They also had higher BMI (29 (95% CI 25–33) vs 25 (95% CI 25–26), *P* = .08) and drank more alcohol (65 g/wk (95% CI 11–119) vs 18 g/wk (95% CI 7–29), *P* = .09). These differences were not significant, but are still interesting considering the small number of patients. Age at SVR was not significantly different between the two groups: 49 years (95% CI 38–60) vs 52 years (95% CI 50–54), *P* = .6. Six patients were diagnosed with hepatocellular carcinoma (HCC) after inclusion in this study. Three of these had a LSM value < 9.5 kPa at follow–up. The characteristics of these patients are presented in .

Table 3. Characteristics of the patients with sustained virological response that developed hepatocellular carcinoma after measurement with liver stiffness at follow–up visits

No	Pre treatment fibrosis stage	Age at SVR (y)	Follow–up time (y)	Liver stiffness (kPa)	DM at follow–up	APRI score at follow–up	BMI at follow–up (kg/m^2)	Alcohol use at follow–up (g/wk)	Time from SVR to HCC (y)
1	F4	64	12.7	10.1	No	0.24	26.5	0	15.1
2	F4	57	14.3	7.4*	No	0.37	28.6	0	15.2
3	F4	56	12.0	13.7	No	0.42	27.7	287	12.8
4	F4	65	0.6	4.8*	Yes	0.3	27.2	0	1.6
5	F3	51	11.6	5.6*	No	0.27	24.1	18	11.6
6	F4	54	0.6	48	Yes	3.21	27.3	0	1.9

SVR, sustained virological response; DM, diabetes mellitus; HCC, hepatocellular carcinoma; BMI, body mass index.
Three patients had liver stiffness values < 9.5 kPa (*) at these visits and later developed HCC. Pretreatment fibrosis is staged according to METAVIR.

Discussion

The long–term effect of achieved SVR on liver fibrosis in patients with HCV–induced advanced fibrosis has not been extensively investigated. To study this, fibrosis in our patients was assessed by LSM during long–term follow–up over more than 5–10 years. Our study shows that the vast majority of our 269 patients with pretreatment advanced fibrosis or cirrhosis improved their fibrosis during long–term follow–up after SVR. A minority, however, continued to have advanced fibrosis even after more than 5–10 years of follow–up. In this subset of patients, a point of no return for advanced liver fibrosis might have been reached, where improvement is not possible. Other possible explanations are contributing cofactors such as liver steatosis with inflammation and alcohol use as driving forces to maintain or even progress liver fibrosis. In this study, we identified pretreatment cirrhosis, high age and high BMI as the main risk factors for lack of improvement. The proportion of patients who

maintained advanced fibrosis decreased among patients with longer follow–up time, indicating that fibrosis regression is a slow process that continues over time.

Several studies with varying follow–up times have compared pre– and post–treatment fibrosis stages.[10,19–27] Studies based on liver biopsies have all shown that fibrosis and also cirrhosis can improve after achievement of SVR in a majority of patients, but also that fibrosis will persist or progress after SVR in a subset of 1%–14%, confirming the results in our study.[19–23] In a large study including more than 3000 biopsied patients with a mean follow–up time of 20 months, a low baseline fibrosis stage, age below 40 and BMI below 27 were all factors strongly associated with lack of significant fibrosis at follow–up in patients with SVR.[19] The risk factors identified to be associated with persisting fibrosis found were the same as in our long–term study.

More recent studies have investigated fibrosis regression after SVR with LSM and biochemical markers. The diagnostic accuracy of these methods to detect persisting cirrhosis after SVR, however, has been questioned.[10,24] In a study comparing LSM with follow–up biopsies 61 months after achieved SVR, the sensitivity of LSM to detect cirrhosis after SVR was only 61% when standard pretreatment cut–offs were used.[10] On the other hand, the specificity for diagnosing cirrhosis with LSM after treatment reached 95%. As LSM measures both fibrosis and inflammation, rapid early improvement of liver stiffness after SVR could be explained by a reduction in liver inflammation, and not by fibrosis regression. This could suggest that patients with pretreatment cirrhosis defined by LSM, including some with severe inflammation and less advanced fibrosis, would have lower liver stiffness at follow–up than patients with biopsy–proven cirrhosis. Surprisingly, in our study, we observed the opposite. The difference was not significant, but could be explained by the fact that patients with cirrhosis defined by LSM had shorter follow–up times. This supports our conclusion that cirrhosis regression is a process that continues over time. Recently published studies with repeated LSM up to 2 years after achieved SVR have shown a rapid initial improvement of liver stiffness, but also a continued slower reduction, better reflecting true fibrosis regression.[25–27] The follow–up times in these studies were relatively short, but the findings support the results generated in our study. Another possible explanation for the initial rapid and later slower improvement of liver stiffness levels after SVR could be the remaining presence of nodular architecture in the liver, despite decreased amount of fibrosis.[21] Nodules are the hallmark for a histopathological definition of cirrhosis.[5] This implies that the persisting advanced fibrosis in our study, measured by LSM, probably is accurate, while we might have misclassified the stage of fibrosis in some of the cirrhotic patients that still had nodular architecture.

Although this study was not designed to assess the correlation between LSM and the risk to develop HCC, there were patients in our study with improved fibrosis who later developed HCC up to 15 years after SVR. This finding supports that surveillance for HCC should continue even in patients where cirrhosis has regressed after achieved SVR. The duration for such surveillance needs to be further studied. We have earlier found that diabetes and the presence of pretreatment cirrhosis were risk factors for the development of HCC after SVR had been achieved.[13] No direct correlation between diabetes mellitus and persisting advanced fibrosis was noted in this study. On the other hand, high BMI, known to be associated with diabetes, was found to be a risk factor for persisting advanced fibrosis.

There are several limitations to this study. It had a cross–sectional and retrospective design and lacked sequential LSMs for the included patients. However, in a preliminary prospective study on LSM data collected at 6–month intervals after SVR in 100 patients with F3–F4 fibrosis at baseline, 31% had persisting advanced fibrosis, similar to the results in our study.[28] Furthermore, in our study, a third of the eligible patients were excluded or lost to follow–up, which could introduce a selection bias. Baseline characteristics for the nonincluded patients were, however, comparable to the studied patients, reducing this bias. The clinical outcome was worse in the excluded group with higher occurrence of HCC and death, but the causes of death were not liver related in a majority of the cases.

Assessment of fibrosis after SVR with transient elastography and not liver histology may have caused us to underestimate the extent of advanced fibrosis at follow–up. However, the identified patients with maintained advanced fibrosis are probably correctly classified. As all our patients were treated with IFN–based regimens, we do not know if our findings are relevant for patients treated with IFN–free regimens. One recently published study, however, showed a statistically similar median change in LSM levels 24 weeks after the end of treatment in patients with SVR after IFN–containing and IFN–free regimens.[25]

To conclude, we found that the liver fibrosis after achievement of SVR improved in the vast majority of our patients after long–term follow–up. Our data indicate that fibrosis regression is an ongoing long–term process over years. Risk factors for lack of such improvement during follow–up were pretreatment cirrhosis, older age and high body mass index. Lifestyle intervention to decrease weight in obese persons and treatment before establishment of cirrhosis at a younger age should therefore be recommended to avoid persistence of advanced fibrosis after SVR.

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Abbreviations

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FU, follow-up; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LSM, liver stiffness measurement; OR, odds ratio; SVR, sustained virological response.

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