







Dysmetabolism, Diabetes and Clinical Outcomes in Patients Cured of Chronic Hepatitis C: A Real-Life Cohort Study

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The aim of this study was to examine the impact of features of dysmetabolism on liver disease severity, evolution, and clinical outcomes in a real-life cohort of patients treated with direct acting antivirals for chronic hepatitis C virus (HCV) infection. To this end, we considered 7,007 patients treated between 2014 and 2018, 65.3% with advanced fibrosis, of whom 97.7% achieved viral eradication (NAVIGATORE-Lombardia registry). In a subset (n = 748), liver stiffness measurement (LSM) was available at baseline and follow-up. Higher body mass index (BMI; odds ratio [OR] 1.06 per kg/m², 1.03-1.09) and diabetes (OR 2.01 [1.65-2.46]) were independently associated with advanced fibrosis at baseline, whereas statin use was protective (OR 0.46 [0.35-0.60]; *P* < 0.0001 for all). The impact of BMI was greater in those without diabetes (*P* = 0.003). Diabetes was independently associated with less pronounced LSM improvement after viral eradication (*P* = 0.001) and in patients with advanced fibrosis was an independent predictor of the most frequent clinical events, namely *de novo* hepatocellular carcinoma (HCC; hazard ratio [HR] 2.09 [1.20-3.63]; *P* = 0.009) and cardiovascular events (HR 2.73 [1.16-6.43]; *P* = 0.021). Metformin showed a protective association against HCC (HR 0.32 [0.11-0.96]; *P* = 0.043), which was confirmed after adjustment for propensity score (*P* = 0.038). Diabetes diagnosis further refined HCC prediction in patients with compensated advanced chronic liver disease at high baseline risk (*P* = 0.024). **Conclusion:** Metabolic comorbidities were associated with advanced liver fibrosis at baseline, whereas statins were protective. In patients with advanced fibrosis, diabetes increased the risk of *de novo* HCC and of cardiovascular events. Optimization of metabolic comorbidities treatment by a multi-disciplinary management approach may improve cardiovascular and possibly liver-related outcomes. (*Hepatology Communications* 2022;6:867-877).

Chronic hepatitis C (CHC) remains a leading cause of liver disease worldwide. However, direct acting antivirals (DAAs) have revolutionized hepatitis C virus (HCV) treatment with simple, tolerable, pan-genotypic combinations that currently achieve cure rates exceeding 95%

Abbreviations: ASA, acetylsalicylic acid; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CHC, chronic hepatitis C; CI, confidence interval; CVE, cardiovascular events; DAA, direct acting antiviral; F, female; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HR, hazard ratio; LSM, liver stiffness measurement; NS, not significant; OR, odds ratio; SVR, sustained virological response; US, ultrasonography.

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in a few weeks.⁽¹⁾ This progress has allowed us to treat most patients in follow-up in developed countries, reducing the burden of CHC-related end-stage liver disease.⁽²⁾ Sustained virological response (SVR) to DAA treatment corresponds to the cure of HCV infection, and in patients without severe portal hypertension this results in a reduction of hepatic fibrosis and a decrease in the risk of liver-related and all clinical events at follow-up.⁽³⁻⁵⁾ However, in individuals who had already developed advanced fibrosis at the time of cure, some complications such as hepatocellular carcinoma (HCC) development remain a major threat.^(6,7)

Among the drivers of liver injury that can persist after HCV eradication, fatty liver plays a prominent

role,⁽⁷⁾ through the induction of lipotoxicity and steatohepatitis.⁽⁸⁾ However, uncertainties remain on the burden of metabolic comorbidities, in particular of diabetes and obesity, in patients with advanced liver fibrosis who cleared HCV.⁽⁷⁾ Furthermore, the impact of dysmetabolism and of the treatments for metabolic comorbidities on the relative risk of hepatic and cardiovascular events (CVEs) has never been reported in large real-life cohorts.

Within this context, the aim of this study was to examine the impact of dysmetabolism features (diabetes, overweight, and the presence of any of these features or fatty liver) and of pharmacological therapy on liver disease severity and evolution, and on follow-up liver-related and CVEs, in a real-life cohort

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of patients treated with DAAs representative of an entire European region (NAVIGATORE-Lombardia Network registry).

Experimental Procedures

STUDY COHORT

Data of all patients with CHC treated with DAAs in the Lombardy region in Northern Italy, starting from December 2014 to December 2018 in 48 different clinical centers, were collected through the NAVIGATORE Lombardia Network web-based platform, which is based on REDCap (Research Electronic Data Capture; <http://projectredcap.org>).⁽⁹⁾ Recruitment procedures and disease staging are reported in the Supporting Methods.^(10,11) Briefly, liver fibrosis was staged in all patients before DAA treatment, either by liver biopsy (METAVIR stage) or noninvasively by transient elastography. Liver stiffness measurement (LSM) thresholds are reported in the Supporting Methods. Patients with decompensated cirrhosis were allocated to fibrosis stage F4.⁽¹⁰⁾ After data retrieval and revision of the database by visual data inspection, we selected 7,007 (74.0%) of 9,470 for whom age, sex, anthropometric features, fibrosis staging, metabolic comorbidities, and pharmacological treatment were available (main study cohort). In 748 (10.7%), systematic LSM re-evaluation at 24 weeks following treatment was performed. Among 4,578 patients with advanced fibrosis, follow-up data were available for 2,946 individuals at 24 weeks and for 1,905 at 24 months following treatment (64.4% and 41.6% respectively; Prospective cohort). CVEs were defined as stroke, myocardial infarction, hospitalization due to ischemic heart disease or heart failure, and sudden death.

In a second phase, we collected data relative to the presence of ultrasonography (US) bright liver in a subset of 2,723 of 3,507 patients with cirrhosis (77.6%), from 21 participating centers. In this subset (US cohort), presence of fatty liver was defined by US after confirmation of SVR.⁽¹¹⁾ To further test the clinical relevance of the findings, we tested the ability of dysmetabolic features to refine risk stratification of *de novo* HCC in patients who cleared HCV infection with compensated advanced chronic liver disease (cACLD), where risk stratification was assessed based

on follow-up LSM and albumin values (reported in detail in the Supporting Methods).⁽¹²⁾

The clinical features of patients included in the main study cohort are presented in Table 1. The study flowchart is presented in Fig. 1. Informed consent was obtained from each patient, and the registry was approved by the ethical committees and review boards of the participating centers and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study analysis plan was approved by the Ethics Committee of the University of Milan (on October 23, 2018).

STATISTICAL ANALYSIS

For descriptive statistics, categorical variables are shown as number and proportion, while continuous variables are shown as mean and SD or median and interquartile range (IQR), as appropriate.

Observational associations were performed by fitting data to generalized linear models. Logistic regression models were fit to examine binary traits, and the association between metabolic risk factors and liver disease stage/clinical outcomes was adjusted for the covariates specified in the text. The product terms of significant predictors were tested in multivariable generalized linear models to survey for interactions in determining the risk of advanced fibrosis. The impact of dysmetabolism on survival was assessed by log-rank test, whereas the independent predictors of clinical events were assessed by multivariable Cox regression proportional hazard models. As the main study aim was to examine the impact of metabolic comorbidities and their treatments on the clinical outcomes, we included as covariates in multivariable models demographic features (age, sex), body mass index (BMI), presence of diabetes, use of drugs potentially affecting outcomes (statins and metformin, when significant at univariate analysis), the main clinical risk factors associated with the specific outcomes at univariate analysis (detailed in the Results section and tables), and variables significantly associated with the outcome at univariate analysis. The association between metformin exposure and *de novo* HCC development was adjusted for propensity score, as reported in the Supporting Methods.

Statistical analysis was carried out using the JMP 16.0 Pro Statistical Analysis Software (SAS Institute, Cary, NC) and R statistical analysis software version

TABLE 1. CLINICAL FEATURES OF 7,007 PATIENTS FROM THE NAVIGATORE-LOMBARDIA COHORT (MAIN STUDY COHORT) WITH COMPLETE BASELINE CLINICAL DATA STRATIFIED BY FIBROSIS SEVERITY

	Advanced Fibrosis		P Value
	No (Stage F0-F2)	Yes (Stage F3-F4)	
n	2,429 (34.7)	4,578 (65.3)	
Age, years	60.1 ± 13.4	61.9 ± 12.2	<0.0001
Sex, F	1,187 (48.9)	1,784 (39.0)	<0.0001
BMI, kg/m ²	24.2 ± 3.9	25.3 ± 4.2	<0.0001
Alcohol use, yes	402 (16.6)	816 (17.8)	0.18
HCV genotype			<0.0001
G1	1,355 (55.8)	2,724 (59.5)	
G2	604 (24.9)	688 (15.0)	
G3	240 (9.9)	661 (14.4)	
G4	210 (8.6)	488 (10.7)	
Other	3 (0.1)	13 (0.1)	
NA	17 (0.7)	6 (0.3)	
Fibrosis, stage	0: 455 (18.7)	3: 1,071 (23.4)	<0.0001
	1: 1,126 (46.4)	4: 3,507 (76.6)	
	2: 848 (34.9)		
FIB-4 score	1.9 ± 2.1 (n = 2,204)	5.0 ± 4.4 (n = 4,085)	<0.0001
LSM, kPa	6.3 ± 1.9 (n = 2,272)	19.9 ± 11.1 (n = 3,849)	<0.0001
HBV, HBcAg or HBsAg+	622 (27.7)	1,243 (30.7)	0.011
HIV+	245 (10.0)	790 (17.1)	<0.0001
Body weight			<0.0001
Underweight (<20 kg/m ²)	270 (11.1)	314 (6.7)	
Normal weight (20-25 kg/m ²)	1,308 (53.8)	2,148 (46.9)	
Overweight (25.1-29.9 kg/m ²)	653 (26.9)	1,658 (34.2)	
Obese (≥30 kg/m ²)	198 (8.1)	549 (12.0)	
Treated diabetes	147 (6.0)	571 (12.5)	<0.0001
Treated hypertension	751 (30.9)	1,581 (34.5)	0.002
Statin therapy	133 (5.3)	136 (3.0)	<0.0001
Treated hypertriglyceridemia	23 (1.0)	32 (0.7)	0.26

Note: Data are shown as mean ± SD or n (%) values, as appropriate. Abbreviations: F, female; FIB-4, Fibrosis-4 index; HBcAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen.

3.5.2 (<http://www.R-project.org/>). *P* values < 0.05 (two-tailed) were considered significant.

Results

INDEPENDENT DETERMINANTS OF ADVANCED FIBROSIS AND OF FIBROSIS REGRESSION

The clinical features of patients in the main study cohort stratified by the presence of advanced fibrosis are reported in Table 1, Supporting Results, and Supporting Fig. S1. The prevalence of obesity according

to fibrosis stage and diabetes status is shown in Fig. 2; obesity was more frequently detected in patients with diabetes than in those without (*P* < 0.0001), and its prevalence increased progressively with fibrosis stage both in the overall cohort and in patients without diabetes (*P* < 0.0001). The variables independently associated with advanced fibrosis are reported in Table 2. Age was the variable most strongly associated with advanced fibrosis, followed by HCV genotype (G3>G1>G2), BMI, human immunodeficiency virus (HIV) co-infection, and diabetes (*P* < 0.0001 for all). A significant interaction between BMI and diabetes (but not between other independent predictors) on the risk of advanced fibrosis was observed, in that

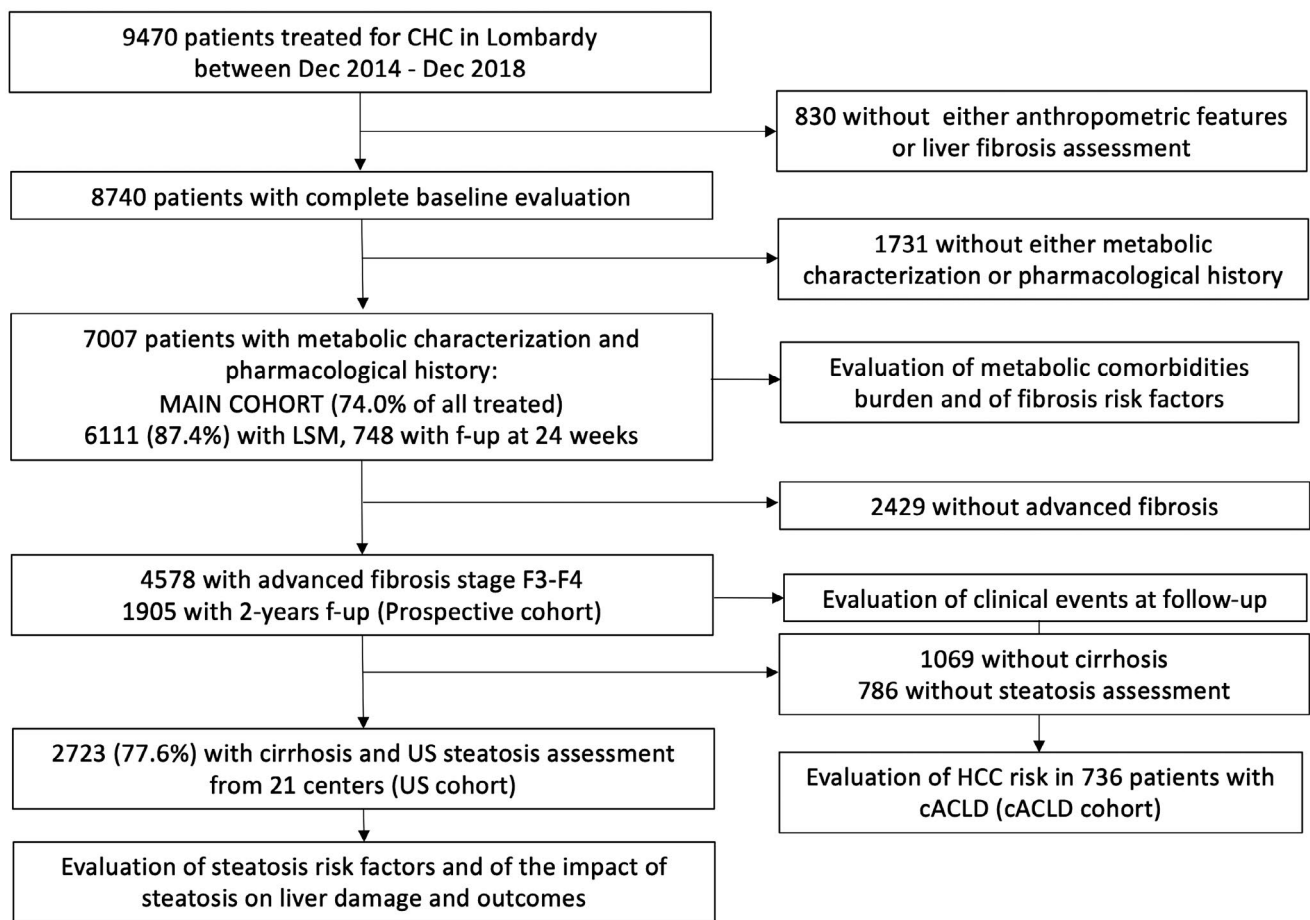


FIG. 1. Study flow chart.

the protective impact of lower BMI was attenuated in those with diabetes (interaction term reported in Table 1; $P = 0.003$).

Conversely, statin therapy was independently and inversely associated with advanced fibrosis (Table 2; $P < 0.0001$) and LSM values (11.9 ± 8.6 vs. 14.9 ± 11.1 kPa; $P < 0.0001$). Sensitivity analyses are reported in the Supporting Results and Tables S1-S2.

SVR was achieved by 6,849 participants (97.7%). Lack of SVR was independently associated with infection by HCV-G3, advanced fibrosis, and male sex, but not with metabolic risk factors nor with statin use (Supporting Table S3). The independent determinants of fibrosis progression in patients with available paired LSM evaluation at baseline and 24 weeks following treatment are given in Table 3. After adjustment for baseline values and the main clinical covariates, LSM tended to decrease in patients who achieved SVR (estimate -0.191

± 0.088 ; $P = 0.029$), but less so in those affected by diabetes (estimate $+0.047 \pm 0.023$; $P = 0.039$).

IMPACT OF DIABETES ON CLINICAL EVENTS IN PATIENTS WITH ADVANCED FIBROSIS

The impact of features of dysmetabolism on clinical events, and variables associated with fatty liver in patients with cirrhosis, are presented in the Supporting Results, Table S5, and Fig. S1. The most frequent clinical event was HCC development, followed by CVEs and ascites (incidence rates 2.2%, 1.9% and 0.3%, respectively).

During follow-up, 80 of 425 (18.8%) patients with previous HCC had a relapse, whereas 145 of 4,178 (3.5%) of patients with advanced fibrosis developed *de novo* HCC. The independent determinants of HCC

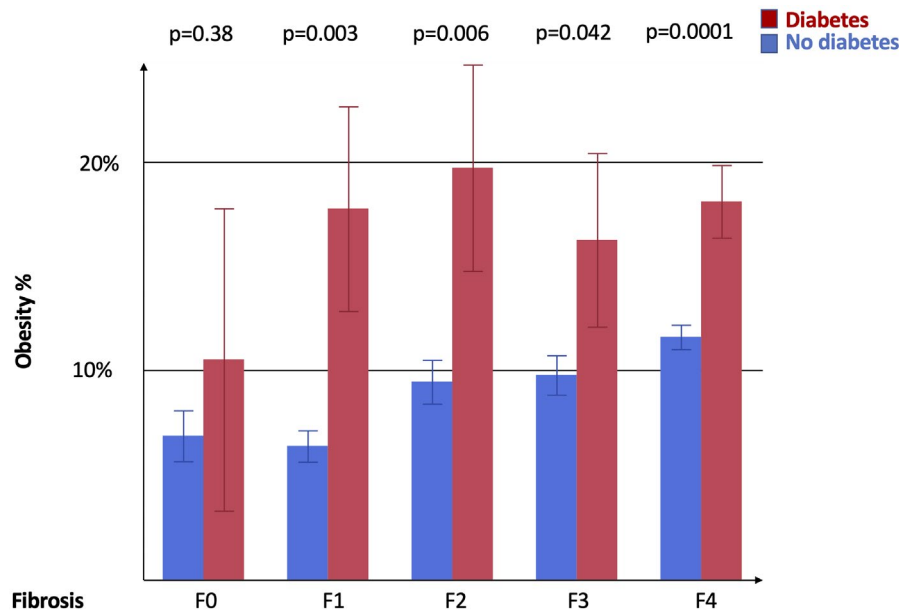


FIG. 2. Prevalence of obesity in patients stratified by fibrosis stage and diabetes diagnosis. Data are shown as % and SEM. $P < 0.0001$ for increased prevalence of obesity with fibrosis stage severity in the overall cohort and patients without diabetes (age and sex adjusted); $P = \text{NS}$ in patients with diabetes; and $P < 0.05$ for the higher prevalence of obesity in diabetes versus without diabetes across fibrosis stages F0-F4 (age and sex adjusted).

TABLE 2. VARIABLES INDEPENDENTLY ASSOCIATED WITH ADVANCED FIBROSIS (STAGE F3-F4) AT BASELINE AT MULTIVARIABLE LOGISTIC REGRESSION ANALYSIS (N = 7,007)

	OR	95% CI	PValue
Age, 10 years	1.33	1.28-1.38	<0.0001
Sex, F	0.68	0.61-0.77	<0.0001
HCV genotype, vs. 1	2: 0.50	0.44-0.58	<0.0001
	3: 1.52	1.28-1.81	
	4: 1.18	0.98-1.41	
HBV, yes	0.98	0.87-1.11	0.76
HIV, yes	2.10	1.77-2.48	<0.0001
BMI*, kg/m ²	1.07	1.06-1.09	<0.0001
Hypertension, yes	1.04	0.92-1.17	0.53
Diabetes*, yes	2.01	1.65-2.46	<0.0001
Statins, yes	0.46	0.35-0.60	<0.0001
Treated hypertriglyceridemia, yes	0.78	0.44-1.38	0.39
Alcohol use, yes	0.98	0.85-1.14	0.34

Note: Analyses were conducted a multivariable generalized linear model adjusted for the independent variables shown in the table plus liver transplantation.

*Estimate. -0.03 ± 0.01 ($P = 0.003$) for the BMI \times diabetes interaction term ($[\text{BMI}-24.88] \times \text{diabetes}$), meaning that the impact of overweight was significantly larger in those without a diabetes diagnosis.

Abbreviation: HBV, hepatitis B virus.

TABLE 3. INDEPENDENT PREDICTORS OF LSM CHANGES AT 24-WEEK FOLLOW-UP AFTER THERAPY IN 748 PATIENTS WITH COUPLED EVALUATIONS

Term	Estimate	SEM	PValue
Sex, F	+0.008	0.016	0.63
Age, 10 years	+0.010	0.012	0.44
SVR, yes	-0.191	0.088	0.029
BMI, kg/m ²	+0.002	0.004	0.57
Diabetes, yes	+0.047	0.023	0.039

Note: A multivariable generalized linear model adjusted for the variants reported in the table and baseline LSM values.

risk during follow-up in all patients with advanced fibrosis are given in Supporting Table S6. Among patients with previous HCC, 80 (20.9%) recurred after a median of 14 (IQR 1-24) months. The independent determinants of *de novo* HCC in patients with advanced fibrosis in the Prospective cohort are provided in Table 4, upper panel. Development of *de novo* HCC was independently associated with lack of SVR ($P < 0.0001$), older age ($P = 0.0002$), male sex

TABLE 4. INDEPENDENT DETERMINANTS OF THE RISK OF DEVELOPMENT OF *DE NOVO* HCC (N = 145) AND CVEs (N = 53) IN PATIENTS WITH CHC WITH ADVANCED FIBROSIS

	HR	95% CI	PValue
<i>De Novo</i> HCC (n = 4,178 at risk)			
Age, years	1.04	1.02-1.06	0.0002
Sex, F	0.60	0.39-0.92	0.020
HCV, G3 vs. other	1.80	1.09-2.96	0.021
SVR, yes	0.28	0.16-0.49	<0.0001
Cirrhosis vs. fibrosis F3	7.65	1.07-54.84	0.043
BMI, kg/m ²	1.01	0.97-1.06	0.59
Diabetes, yes	2.09	1.20-3.63	0.009
Metformin, yes	0.32	0.11-0.96	0.042
CVEs (n = 4,578 at risk)			
Age, years	1.04	1.00-1.08	0.035
Sex, F	0.55	0.24-1.23	0.14
BMI, kg/m ²	1.06	0.98-1.15	0.13
HIV, yes	2.75	1.18-6.46	0.020
Diabetes, yes	2.73	1.16-6.43	0.021
Metformin, yes	0.50	0.13-1.95	0.32
Treated hypertension, yes	1.78	0.89-3.19	0.11
Statin, yes	4.85	1.81-13.0	0.0016
ASA, yes	2.27	0.95-5.38	0.063

Note: A multivariable Cox proportional hazard model analysis adjusted for the covariates reported in the table.

($P = 0.020$), infection by HCV-G3 ($P = 0.021$), and cirrhosis ($P = 0.043$). HCC risk was higher in patients with diabetes ($P = 0.009$), whereas it was lower in those taking metformin ($P = 0.042$). Conversely, we did not detect any impact of BMI ($P =$ not significant [NS]), nor of acetylsalicylic acid (ASA) use ($P =$ NS) or of statin treatment (regardless of statin class; Supporting Table S6, upper panel).

The combined impact of diabetes diagnosis and metformin treatment on the incidence of *de novo* HCC in patients with cirrhosis is shown in Fig. 3. HCC incidence was higher in patients with diabetes not taking metformin than in those without diabetes ($P = 0.0015$) and in those with diabetes taking metformin ($P = 0.018$). Exposure to metformin remained associated with protection against development of *de novo* HCC even after adjustment for propensity score (hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.07-0.87; $P = 0.029$; Supporting Table S7). The protective association remained significant even after restricting this

analysis to patients with diabetes (HR 0.22, 95% CI 0.06-0.82; $P = 0.024$).

To further evaluate the clinical relevance of these findings, we examined whether diabetes diagnosis could improve HCC risk stratification based on evaluation of LSM and serum albumin levels following SVR in 536 patients with compensated alcohol-associated liver disease, 305 (56.9%) being classified as at high risk (cACLD cohort; Fig. 4). We first validated the score for prediction of HCC risk ($P = 0.009$; Fig. 4A). Reclassification of high-risk patients according to diabetes (Fig. 4B) highlighted a higher HCC risk in those with diabetes ($n = 43$, 8.0%) as compared to those at low risk ($P < 0.0001$) and to those at high risk without diabetes ($P = 0.024$).

The independent determinants of CVEs ($n = 53$) in the Prospective cohort are provided in Table 4, lower panel. CVEs were associated with being in treatment with statins ($P = 0.0016$), HIV infection ($P = 0.020$), diabetes ($P = 0.021$), and older age ($P = 0.035$). There was a trend for association between ASA use and higher CVE risk ($P = 0.063$), whereas sex, smoking status, treated hypertension, and SVR achievement had no significant impact ($P =$ NS). There was no significant difference in the impact on CVE between hydrophilic and lipophilic statins (Supporting Table S6, lower panel; $P = 0.79$).

Discussion

In this study, we examined the impact of the features and treatments of dysmetabolism on the severity and evolution of liver damage in a real-life cohort representative of patients with CHC treated with DAAs in a large region of Northern Italy.

First, we confirmed that adiposity and diabetes are robustly associated with the development of advanced fibrosis, which is likely partly mediated by fatty liver.⁽¹³⁾ One finding was that the impact of higher BMI was less marked in patients with diabetes. The role of viral factors is discussed in the Supporting Discussion. As most patients with type 2 diabetes have marked insulin resistance regardless of body weight, these data are in line with the notion that insulin resistance leading to hepatic fat accumulation is the main mechanism underlying the association between dysmetabolism and fibrosis.

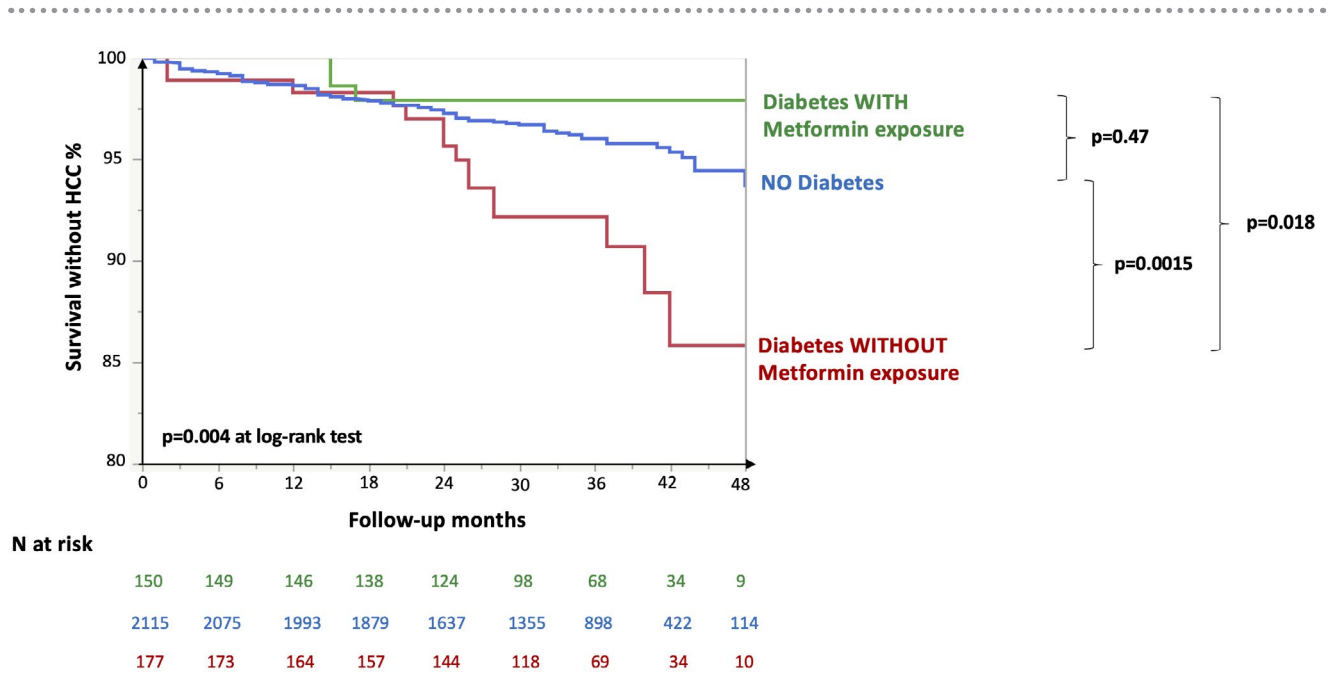


FIG. 3. Impact of diabetes and metformin therapy on the incidence of *de novo* HCC in 2,442 patients with cirrhosis. *P* values are shown at log-rank test.

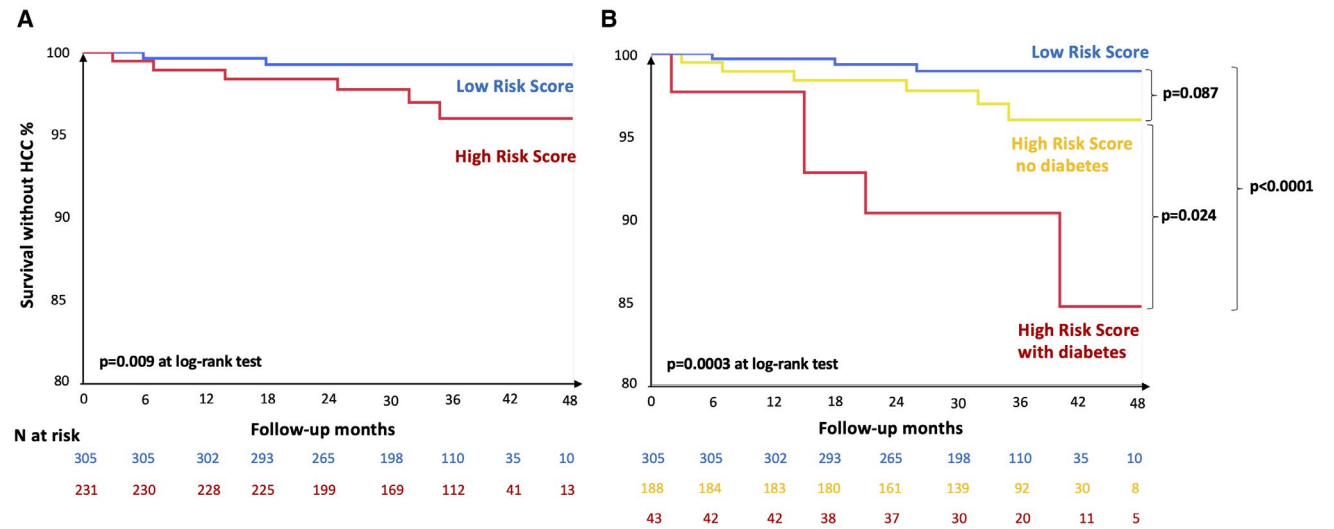


FIG. 4. Impact of diabetes on the reclassification of HCC risk in 536 patients with cACLD. We considered patients with LSM > 10 kPa at baseline, who achieved viral eradication, with compensated liver disease, no previous history of HCC, and re-evaluation of LSM and serum albumin at follow-up. HCC risk was evaluated according to Pons et al.⁽¹²⁾ Patients with LSM ≥ 20 kPa at follow-up and those with LSM = 10-20 kPa and albumin levels < 4.4 g/dL at follow-up were classified as at higher risk. *P* values are shown at log-rank test.

Approximately 1 in 8 patients with advanced fibrosis cured from HCV had diabetes.

Second, after taking into account the impact of pharmacological treatment, we confirmed that diabetes, but not BMI, affects the evolution of liver damage

after viral eradication.^(6,7,14-16) In a subset with systematic re-evaluation at 24 weeks after treatment, diabetes was independently associated with reduced improvement of LSM, which correlated with liver-related events after SVR.⁽¹⁷⁾ In patients with advanced

fibrosis, diabetes was an independent predictor of the two main clinical events at follow-up, i.e., development of *de novo* HCC and of CVE. Although previous studies conducted in smaller cohorts of patients with CHC treated with DAAs often failed to detect a significant impact of diabetes on HCC,⁽¹⁸⁻²¹⁾ our data suggest that patients with diabetes should be prioritized for HCC surveillance, as well as for multidisciplinary management to prevent non-liver-related events. Supporting the clinical relevance of these findings, the presence of diabetes was able to refine HCC risk prediction in patients with cACLD at high baseline risk, based on noninvasive evaluation by LSM and serum albumin after SVR.⁽¹²⁾ In contrast, a more comprehensive definition of dysmetabolism encompassing diabetes, overweight, or the presence of fatty liver was not useful to improve risk stratification of clinical events.

Notably, in the present cohort, patients with advanced fibrosis and diabetes displayed a low use of key drugs prescribed for CVE prevention. The prevalence of statin treatment was approximately 14% in those with diabetes and arterial hypertension. Lack of prescription despite the likely presence of clinical indication did not appear to be justified by the severity of liver damage, as fibrosis stage and liver enzymes were not significantly different between treated and untreated individuals. On the other hand, the impact of HCV replication and of severe liver disease on the reduction of circulating lipid levels may have represented a factor determining low treatment uptake, especially before SVR.^(22,23)

Third, pharmacological treatments for metabolic comorbidities were associated with protection against the main investigated outcomes. Statin use was robustly associated with protection against advanced fibrosis, which persisted even considering only patients without cirrhosis (stage F3 fibrosis as main outcome), suggesting that the association was not accounted for by a prescription bias. Although in the absence of randomized controlled trials definite conclusions cannot be drawn, evidence in fatty liver disease and CHC is consistent with the notion that statins protect from progressive liver disease, with an effect size consistent with the present results.⁽²⁴⁻²⁶⁾ The mechanisms underpinning this protective association encompass modulation of lipid accumulation, inflammation, and fibrogenesis,⁽²⁷⁾ but potentially also inhibition of HCV replication.⁽²⁸⁾ Of note,

recent data support the safety of statin administration in patients with cirrhosis, with potential benefits that extend to the amelioration of portal hypertension,⁽²⁹⁾ and use of lipophilic statins has been associated with chemoprevention of HCC.⁽³⁰⁾ Possibly due to the limited power, lack of information about treatment duration and dose, and different metabolisms in patients with severe liver disease, we could not appreciate any significant effect of treatment with either with lipophilic or hydrophilic statins on HCC risk during the follow-up. On the other hand, although it may be a marker of less-advanced diabetes and liver dysfunction, exposure to metformin was associated with protection against HCC development independently of cirrhosis and of several clinical confounders in patients with diabetes.⁽³¹⁻³³⁾ These data are consistent with previous evidence of a possible chemopreventive activity of metformin on hepatic carcinogenesis.⁽³¹⁻³³⁾ Of note, the protective association between metformin exposure and *de novo* HCC development persisted after adjustment for propensity score.

Although it was previously reported that HCV eradication may also reduce CVEs,⁽³⁴⁾ no data were yet available on the independent CVE predictors in patients with advanced fibrosis after SVR. Possibly due to the relatively low number of patients who did not achieve SVR, we could not detect a benefit of SVR on CVEs. However, we identified diabetes and HIV coinfection⁽³⁵⁾ as main CVE risk factors. The risk of CVE after viral eradication was higher in patients taking statins, and a similar trend was observed for ASA. Given the overwhelming evidence from randomized trials that statins reduce CVE, this observation is likely accounted by the low rate of treatment uptake, suggesting that in this subgroup those who were under treatment were at very high CVE risk or already had events and were on secondary prevention. Prescription of inadequate drug dosages due to the fear of hepatic adverse events may also contribute to explain these findings.

Finally, we identified BMI, absence of hepatic decompensation and younger age, HIV co-infection, and likely diabetes as risk factors for US fatty liver in patients with cirrhosis. Possibly due to the confounding effect of such predictors of clinical events as advanced disease and aging, which favor burnt-out fatty liver and obscure the identification of fat accumulation by US scan, in the present cohort,

fatty liver diagnosis did not significantly improve risk stratification.

This study suffers from common limitations inherent to large registry database related to the detailed characterization of patients. For example, alcohol intake and comorbidities were self-reported or identified by pharmacological treatment, and although evaluation of the pharmacological history was a strength, the study follow-up was only relatively long and we could not adjust for competing risk of death; the dosage and duration of treatment were not available, nor were measurements of insulin resistance and determination of genetic risk factors for fatty liver disease. Furthermore, the present findings may not be applicable to different populations and health care settings. In particular, despite an increase in prescriptions during the last years, statin use remains lower in Italy and Southern Europe than in Northern European countries, although data obtained in patients with advanced liver fibrosis are scarce.⁽³⁶⁾

In conclusion, metabolic comorbidities are associated with liver disease stage and frequently observed in patients with advanced fibrosis who cleared HCV. In this subset, diabetes, but not obesity nor steatosis, was associated with increased risk of *de novo* HCC and CVE, identifying a subset of patients at higher risk of both hepatic and non-hepatic clinical events, whereas exposure to metformin was protective. In a clinical setting focused on the prevention of hepatic complications of advanced liver fibrosis, management of metabolic comorbidities was likely suboptimal, and complicated by the presence of severe liver disease. Therefore, optimization of the management of metabolic comorbidities in patients with advanced fibrosis by a multi-disciplinary management approach may improve cardiovascular and possibly liver-related outcomes.

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