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Original Article

Dynamic change of metabolic dysfunction-associated steatotic liver disease in chronic hepatitis C patients after viral eradication: A nationwide registry study in Taiwan

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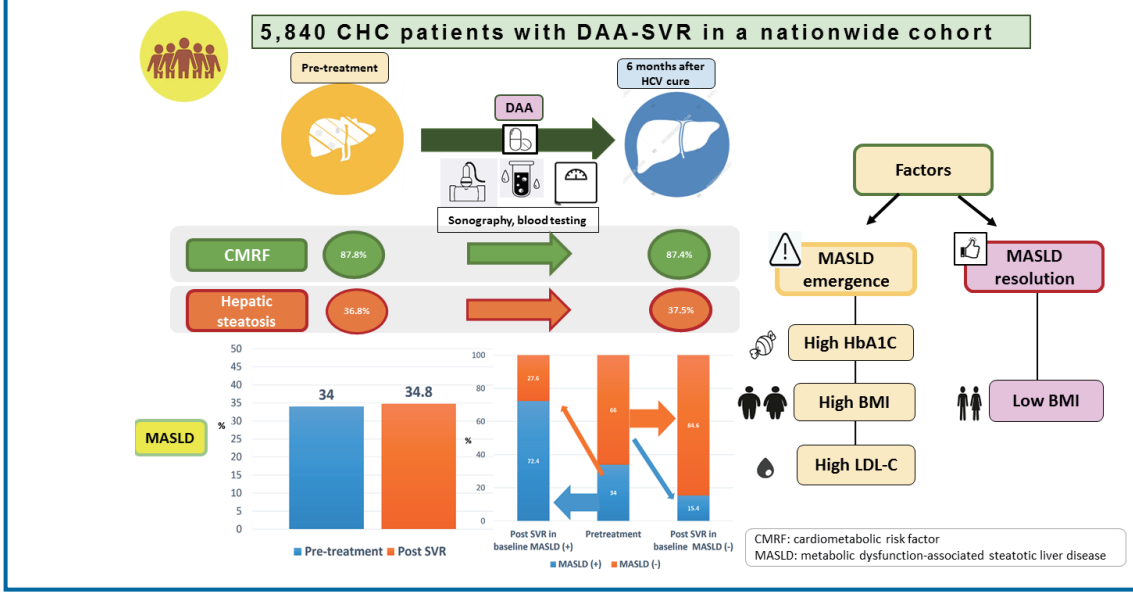
Graphical Abstract



Study Highlights

- CHC patients are prone to develop SLD and express CMRFs. Whether HCV eradication mitigates MASLD status is elusive. Despite the decrease in HbA1c and BMI and the increase in HDL-C and triglycerides after HCV eradication, the proportion of MASLD did not alter significantly. A lower BMI was the factor associated with MASLD resolution. In contrast, unfavorable CMRFs including a higher BMI, LDL-C and HbA1c level were independently associated with MASLD emergence after HCV cure. CMRF surveillance is mandatory for CHC patients with metabolic alterations, which are altered after HCV cure and predict the evolution of MASLD.

Background/Aims: Steatotic liver disease (SLD) is a common manifestation in chronic hepatitis C (CHC). Metabolic alterations in CHC are associated with metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to elucidate whether hepatitis C virus (HCV) eradication mitigates MASLD occurrence or resolution.

Methods: We enrolled 5,840 CHC patients whose HCV was eradicated by direct-acting antivirals in a nationwide HCV registry. MASLD and the associated cardiometabolic risk factors (CMRFs) were evaluated at baseline and 6 months after HCV cure.

Results: There were 2,147 (36.8%) patients with SLD, and 1,986 (34.0%) of them met the MASLD criteria before treatment. After treatment, HbA1c (6.0% vs. 5.9%, P<0.001) and BMI (24.8 kg/m^2 vs. 24.7 kg/m^2, P<0.001) decreased, whereas HDL-C (49.1 mg/dL vs. 51.9 mg/dL, P<0.001) and triglycerides (102.8 mg/dL vs. 111.9 mg/dL, P<0.001) increased significantly. The proportion of patients with SLD was 37.5% after HCV eradication, which did not change significantly compared with the pretreatment status. The percentage of the patients who had post-treatment MASLD was 34.8%, which did not differ significantly from the pretreatment status (P=0.17). Body mass index (BMI) (odds ratio [OR] 0.89; 95% confidence intervals [CI] 0.85–0.92; P<0.001) was the only factor associated with MASLD resolution. In contrast, unfavorable CMRFs, including BMI (OR 1.10; 95% CI 1.06–1.14; P<0.001) and HbA1c (OR 1.19; 95% CI 1.04–1.35; P=0.01), were independently associated with MASLD development after HCV cure.

Conclusions: HCV eradication mitigates MASLD in CHC patients. CMRF surveillance is mandatory for CHC patients with metabolic alterations, which are altered after HCV eradication and predict the evolution of MASLD. **(Clin Mol Hepatol 2024;30:883-894)**

Keywords: HCV; CMRF; SLD; MASLD; SVR

INTRODUCTION

Hepatitis C virus (HCV) infection is prone to insulin resistance, which leads to metabolic disarrangement as one of the extrahepatic manifestations of chronic hepatitis C (CHC). On the other hand, liver steatosis is a common histological feature of CHC. The prevalence of liver steatosis has been reported to be 30% to 70% in CHC patients,[1,2] which is higher than that in patients with other chronic liver diseases and in the general population.[3] At least two types of steatosis are recognized in CHC. Hepatic steatosis in CHC patients infected with genotypes other than genotype 3 (GT3) is mostly due to alterations in host metabolism involving IR (metabolic steatosis). On the other side, steatosis was more common in patients infected with GT3 than in those infected with other HCV genotypes, possibly due to

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Abbreviations:

CHC, chronic hepatitis C; CMRF, cardiometabolic risk factor; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver disease

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direct effects of genotype-specific viral proteins (viral steatosis).[1,4]

HCV eradication improves both liver- and non-liver-related outcomes. For the extrahepatic presentations, the metabolic profiles would be augmented in terms of improvement of glycemic indices.[5,6] Nevertheless, a trade-off in the reversal of hypolipidemia was observed.[7] The modification of hepatic steatosis after HCV eradication has been reported, but the conclusion remained unsettled.[8] Major liver societies have recently proposed the umbrella term of steatotic liver disease (SLD) and the term metabolic dysfunction-associated steatotic liver disease (MASLD) in SLD patients with cardiometabolic risk factors (CMRFs).[9,10] Notably, the frequent presence of CMRFs that increase cardiovascular and hepatic fibrotic risks in CHC patients with hepatic steatosis may be more than a "miscellaneous SLD" and can also be viewed as HCV-MASLD.[11] As metabolic profiles and hepatic steatosis would be augmented after HCV eradication, whether the status of CMRF carriage, SLD and MASLD would have been altered during the postviral eradication period is unclear. The aim of the current study was to address this issue by comparing the status transition before and after viral eradication in a well-characterized CHC cohort.

MATERIALS AND METHODS

Patients were enrolled from a nationwide HCV registry in Taiwan, the Taiwan Association for the Study of the Liver (TASL) HCV Registry program (TACR).[12-14] TACR recruited and followed subjects who received direct-acting antivirals (DAAs) from 2018 to 2022. Patients were excluded if they had unavailable data regarding SLD or CMRFs before and after antiviral therapy, if they had HBV or immunodeficiency virus[15] dual infection, if they failed to achieve a sustained virological response (SVR; defined as undetectable HCV RNA throughout 12 weeks after the end of DAA therapy), or if they reported significant alcohol consumption (>20 g/day for women and >30 g/day for men). This study was approved by the institutional review board of Kaohsiung Medical University Hospital, and it was conducted in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients signed written informed consent forms.

Biochemical analyses were performed on a multichannel autoanalyzer (Hitachi Inc., Tokyo, Japan). HCV RNA and genotypes were measured using a real-time PCR assay (Abbott Molecular, Des Plaines IL, USA; detection limit: 12 IU/mL). Hepatic steatosis was defined by ultrasonography performed by well-trained hepatologists or transient elastography (TE, FibroScan®; Echosens, Paris, France)-based controlled attenuation parameter (CAP) if available. MASLD was defined as having steatotic liver disease in addition to the presence of at least one of the five CMRFs, including (1) body mass index (BMI) ≥23 kg/m^2; (2) fasting plasma glucose ≥100 mg/dL, glycated hemoglobin (HbA1c) ≥5.7% or type 2 diabetes history with or without treatment; (3) blood pressure ≥130/85 mmHg or specific antihypertensive drug treatment; (4) plasma triglycerides ≥150 mg/dL or lipid-lowering treatment; and (5) plasma high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL for males and ≤50 mg/dL for females or lipid-lowering treatment. SLD patients with CMRFs were defined as having HCV-MASLD.[11] We evaluated SLD and CMRFs among the recruited patients before DAA treatment and 6 months after HCV cure.

Statistical analyses

Frequencies were compared between groups using the χ^2 test with Yates' correction or Fisher's exact test. Group means (presented as the mean±standard deviation) were compared using analysis of variance and Student's *t* test or the nonparametric Mann–Whitney test when appropriate. The fibrosis-4 index (FIB-4) was calculated using the following formula: age (years)×aspartate aminotransferase level (AST, U/L)/(platelet count [10^9/L]×alanine transaminase level [ALT, U/L])$^{1/2}$. Paired-t test and McNemar test were used to analyze the changes in the metabolic profiles and the status of CMRFs, SLD and MASLD before and after HCV eradication. Factors with a *P*-value <0.05 in the unadjusted analysis were included in the logistic regression analysis to identify the independent factors associated with MASLD resolution or development. Statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL, USA). All the statistical analyses were based on two-sided hypothesis tests with a significance level of *P*<0.05.

RESULTS

Patients

A total of 5,840 patients were enrolled in the study (Fig. 1). The mean age was 62.7 years, and males accounted for 43.6% of the population. A total of 5,130 (87.8%) patients had at least one of the 5 CMRFs, and 2,147 (36.8%) patients were with SLD.

Compared to patients without SLD, those with SLD were younger, had a higher BMI, and had greater proportions of the female gender, dyslipidemia and CMRF carriage. SLD patients also had higher HCV RNA levels and a smaller proportion of liver cirrhosis. Regarding laboratory data, SLD patients had higher alanine transaminase (ALT) levels and platelet counts and more unfavorable metabolic profiles, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, fasting plasma glucose and HbA1c. These patients also had lower serum creatinine and FIB-4 levels (Table 1).

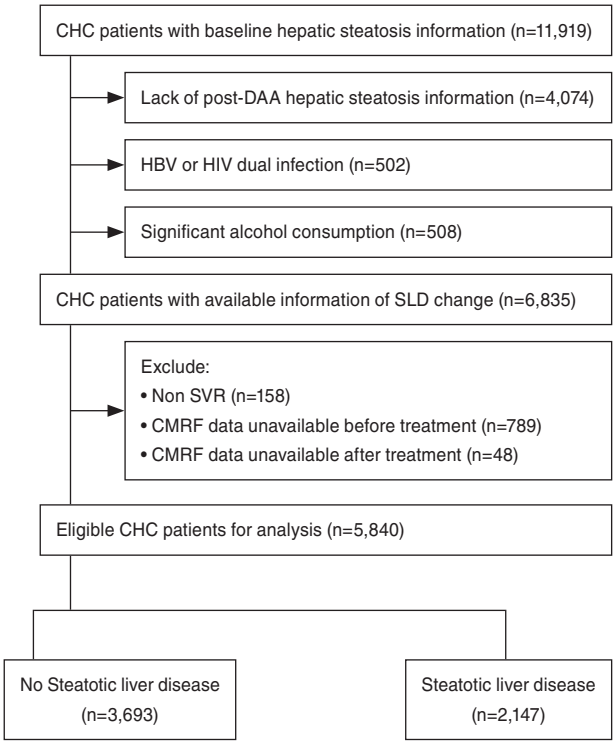

Figure 1. Patient flow chart. SVR, sustained virological response; CHC, chronic hepatitis C; DAA, directly acting antivirals.

Changes in the CMRFs and SLD status after achieving SVR

After HCV eradication, HbA1c (6.0±1.2% vs. 5.9±1.0%, P<0.001) and BMI (24.8±4.0 kg/m^2 vs. 24.7±3.9 kg/m^2, P<0.001) decreased significantly, whereas total cholesterol (172.1+37.0 mg/dL vs. 185.4+39.2 mg/dL, P<0.001), HDL-C (49.1±15.1 mg/dL vs. 51.9±16.7 mg/dL, P<0.001), LDL-C (100.1+31.1 mg/dL vs. 110.3+33.9 mg/dL, P<0.001) and triglycerides (102.8±60.6 mg/dL vs. 111.9±76.0 mg/dL, P<0.001) increased significantly (Table 2). Of the 5,130 patients who had CMRFs before treatment, 96.6% of them remained to have CMRFs and 3.4% became not having CMRF carriage after achieving SVR. On the other hand, of the 710 patients who did not have CMRFs before treatment, 79.6% did not have CMRFs, and 20.6% had CMRFs after achieving SVR. As a result, the portion of the patients who had post-treatment CMRF was 87.4% (5,104/5,840), which did not differ significantly compared to the pretreatment status (P=0.15) (Fig. 2A). The numerical change of CMRFs and factor and case number of individual CMRF disappearance or appearance were shown in Supplementary Table 1 and Supplementary Table 2.

Of the 2,147 patients who had SLD before treatment, 72.5% continued to have SLD, and 27.5% did not have SLD after achieving SVR. On the other hand, of the 3,693 patients who did not have SLD before treatment, 82.8% did not have SLD, and 17.2% developed SLD after achieving SVR. Overall, 37.5% (2,190/5,840) of the patients had post-treatment SLD, which did not significantly differ from the pretreatment status (P=0.22) (Fig. 2B). A total of 1,581 (27.1%) patients had transient elastography available before and after DAA treatment. Of them, the CAP value increased after achieving SVR (230.9±44.8 dB/m, vs. 239.7±49.3 dB/m, P<0.001).

Changes in the MASLD status after achieving SVR

Compared to patients without SLD, those with SLD had a significantly greater proportion of CMRFs (92.5% vs. 85.1%, P<0.001). A total of 1,986 (34.0%) SLD patients possessed at least one CMRF and fulfilled the criteria for MASLD before antiviral treatment. After achieving SVR, 72.4% of the patients still had MASLD, and 27.6% did not

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have MASLD. On the other hand, of the 3,584 patients who did not have MASLD before treatment, 84.6% of them remained to haven't MASLD and 15.4% developed MASLD after achieving SVR. As a result, the portion of the patients who had post-treatment MASLD was 34.8% (2,033/5,840), which did not differ significantly from the pretreatment status (*P*=0.17) (Table 3 and Fig. 2C). Subgroup analysis by stratifying patients with HCV genotype 3 or others, diabetic status, body mass index, cirrhotic status and FIB-4 also did not show a significant change in the proportion of MASLD before or after achieving SVR (Supplementary Table 3).

Factors associated with MASLD resolution or development after achieving SVR

Compared to the patients with persistent MASLD

Table 1. Baseline patient characteristics

Variables	Total (n=5,840)	SLD (-) (n=3,693, 63.2%)	SLD (+) (n=2,147, 36.8%)	*P*-value
Age, years	62.7±12.0	63.6±12.0	61.1±11.7	<0.001
Sex, Male	2,545 (43.6)	1,659 (44.9)	886 (41.3)	0.007
BMI, kg/m^2	24.8±4.0	24.1±3.8	25.9±4.0	<0.001
Smoking	1,015 (17.4)	638 (17.3)	377 (17.6)	0.783
Alcohol use	724 (12.4)	438 (11.9)	286 (13.3)	0.102
Comorbidity				
Diabetes mellitus	1,388 (23.8)	857 (23.2)	531 (24.7)	0.187
Hypertension	2,497 (42.8)	1,565 (42.4)	932 (43.4)	0.442
Hyperlipidemia	867 (14.8)	469 (12.7)	398 (18.5)	<0.001
Coronary artery disease	651 (11.1)	427 (11.6)	224 (10.4)	0.186
Liver cirrhosis	1,967 (33.7)	1,421 (38.5)	546 (25.4)	<0.001
Any one of the 5 CMRFs	5,130 (87.8)	3,144 (85.1)	1,986 (92.5)	<0.001
HCV RNA, $\log_{10}$ IU/mL	5.78±1.04	5.76±1.03	5.82±1.04	0.028
HCV genotype 3	78 (1.3)	48 (1.3)	30 (1.4)	0.754
Laboratory parameters				
AST, IU/L	64.0±51.4	64.8±51.2	62.7±51.7	0.137
ALT, IU/L	74.7±73.3	72.6±73.4	78.2±72.9	0.005
rGT, IU/L	55.2±74.4	54.9±72.2	55.8±77.7	0.723
Platelet count, x10^3/μL	179.0±75.4	169.7±75.9	195.1±71.6	<0.001
Triglyceride, mg/dL	102.8±59.4	96.3±53.4	112.7±66.4	<0.001
Total cholesterol, mg/dL	172.2±37.4	170.1±37.2	175.5±37.5	<0.001
HDL-C, mg/dL	49.1±15.3	50.0±15.8	47.7±14.4	<0.001
LDL-C, mg/dL	99.9±31.1	97.2±30.8	104.0±31.2	<0.001
FPG, mg/dL	110.6±36.1	109.0±33.9	113.1±39.2	0.001
HbA1c, %	6.0±1.2	5.9±1.1	6.1±1.3	<0.001
Creatinine, mg/dL	1.2±1.6	1.2±1.7	1.0±1.4	<0.001
FIB-4	3.6±3.9	4.1±4.4	2.8±2.6	<0.001

Variables are expressed as mean±standard deviation or number (%).
SLD, steatotic liver disease; BMI, body mass index; CMRFs, cardiometabolic risk factors; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGT, r-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FIB-4, fibrosis-4 index.
Directly acting antivirals agents including sofosbuvir (SOF)+ribavirin (RBV) (n=315, 5.4%), ledipasvir (LDV)/SOF+RBV (n=813, 14.2%), paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD)+RBV (n=854, 14.6%), daclatasvir (DCV)/asunaprevir (ASV) (n=263, 4.5%), elbasvir (EBR)/grazoprevir (GZR) (n=539, 9.2%), glecaprevir (GLE)/ pibrentasvir (PIB) (n=1,232, 21.1%), SOF/velpatasvir (VEL) (n=1,585, 27.1%), SOF/DCV (n=158, 2.7%), SOF/VEL/voxilaprevir (VOX) (n=50, 0.9%) and others (n=13, 0.3%).

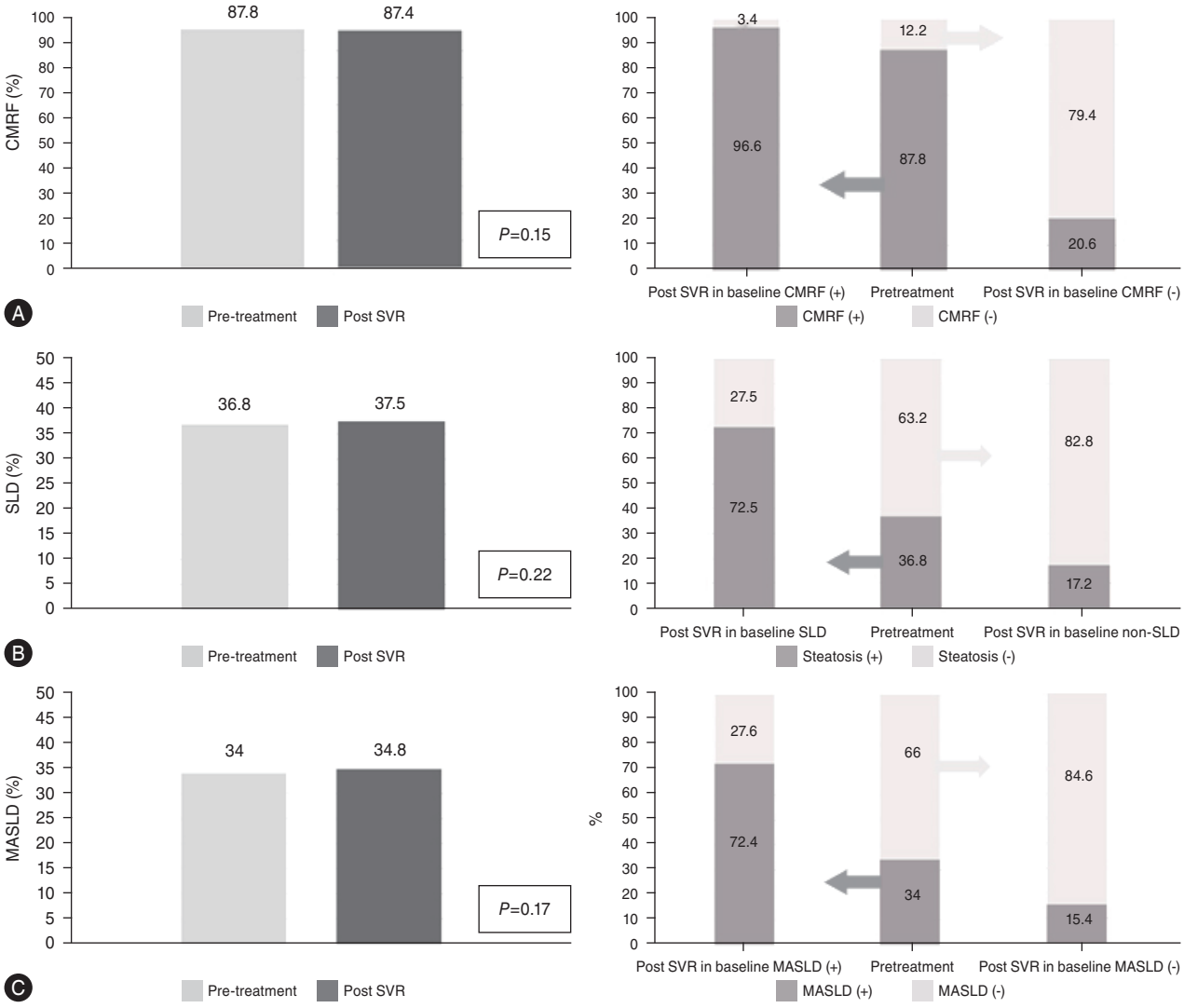

Figure 2. Changes in the CMRFs, SLD and MASLD before and after achieving a sustained virological response (SVR). (A) Changes in the CMRFs. (B) Changes in the SLD. (C) Changes in the MASLD. CMRFs, cardiometabolic risk factors; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

(n=1,438), those who achieved MASLD resolution (n=848) were older; had a lower BMI, platelet counts and HCV RNA level; had a higher pretreatment and post-treatment FIB-4 score; and had a smaller proportion of genotype 3 infection and fewer numbers of CMRF. These patients also had more favorable pretreatment metabolic profiles, including lower triglyceride, LDL-C, fasting plasma glucose, and HbA1c levels and higher HDL-C levels. Logistic regression analysis revealed that BMI (odds ratio [OR] 0.89; 95% confidence intervals [CI] 0.85–0.92; *P*<0.001) was the only factor independently associated with MASLD resolution (Table 4).

On the other hand, compared to the patients with persistent non-MASLD (n=3,259), those who developed MASLD (n=595) were younger; had a higher BMI, platelet counts and HCV RNA level; had a lower pretreatment and post-treatment FIB-4 score; and had a greater proportion of diabetes. They also had more unfavorable pretreatment metabolic profiles, including more numbers of CMRF, higher triglyceride, LDL-C, fasting plasma glucose and HbA1c levels and lower HDL-C levels. Logistic regression analysis revealed that factors independently associated with MASLD development included BMI (OR 1.10; 95% CI 1.06–1.14; *P*<0.001), LDL-C (OR 1.00; 95% CI 1.00–1.01;

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Table 2. Change of cardiometabolic risk factors before and after achieving SVR

Factor	Baseline	Post-SVR	*P*-value
BMI, kg/m^2	24.8±4.0	24.7±3.9	<0.001
>23	3,618/5,514 (65.6)	3,591/5,514 (65.1)	0.021
Fasting glucose, mg/dL	111.4±35.2	110.9±33.3	0.456
>100	1,592/2,849 (55.9)	1,649/2,849 (57.9)	0.027
HbA1c, %	6.0±1.2	5.9±1.0	<0.001
>5.7	1,573/3,197 (49.2)	1,593/3,197 (49.8)	0.365
Total cholesterol, mg/dL	172.1+37.0	185.4+39.2	<0.001
HDL-C, mg/dL	49.1±15.1	51.9±16.7	<0.001
Male≤40, Female≤50	1,342/2,907 (46.2)	1,108/2,907 (38.1)	<0.001
LDL-C, mg/dL	100.1+31.1	110.3+33.9	<0.001
Triglyceride, mg/dL	102.8±60.6	111.9±76.0	<0.001
>150	428/3,191 (13.4)	586/3,191 (18.4)	<0.001

Variables are expressed as mean±standard deviation or number (%).
SVR, sustained virological response; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 3. Change of SLD and CMRF status before and after achieving SVR

Baseline		Post -SVR			
SLD + (n=2,147, 36.8%)	CMRF – (n=161, 7.5%)	SLD –	67 (41.6%)	CMRF –	54 (80.6%)
				CMRF +	13 (19.4%)
		SLD +	94 (58.4%)	CMRF –	65 (69.2%)
				CMRF +	29 (30.8%)
	CMRF + (n=1,986, 92.5%)	SLD –	524 (26.4%)	CMRF –	16 (3.1%)
				CMRF +	508 (96.9%)
		SLD +	1,462 (73.6%)	CMRF –	24 (1.6%)
				CMRF +	1,438 (98.4%)
SLD – (n=3,693, 63.2%)	CMRF – (n=549, 14.9%)	SLD –	479 (87.3%)	CMRF –	397 (82.9%)
				CMRF +	82 (17.1%)
		SLD +	70 (12.7%)	CMRF –	48 (68.6%)
				CMRF +	22 (31.4%)
	CMRF + (n=3,144, 85.1%)	SLD –	2,580 (82.1%)	CMRF –	112 (4.3%)
				CMRF +	2,468 (95.7%)
		SLD +	564 (17.9%)	CMRF –	20 (3.6%)
				CMRF +	544 (96.5%)

SLD, steatotic liver disease; CMRF, cardiometabolic risk factor; SVR, sustained virological response.

P=0.027), and HbA1c (OR 1.19; 95% CI 1.04–1.35; *P*=0.01) (Table 5).

DISCUSSION

In the present study, we demonstrated that more than one-third of CHC patients had SLD, and the majority of them possessed at least one CMRF, indicating that one-third of the CHC patients had HCV-MASLD. Albite that metabolic profiles drastically altered sooner after HCV eradication, the proportion of CMRFs carriage or not did not change significantly per definition.[9,10] Despite a substantial proportion of patients who developed or resolved

Table 4. Factors associated with MASLD resolution in baseline MASLD patients

Variables	MASLD (+)→(–) (n=548, 27.6%)	MASLD (+)→(+) (n=1,438, 72.4%)	*P*-value	Multivariate analysis	
				Odd ratio (95% CI)	*P*-value
Age, years	63.4±11.2	60.8±11.5	<0.001	1.01 (1.00–1.03)	0.097
Sex, Male	219 (40.0)	611 (42.5)	0.308		
Baseline BMI, kg/m^2	25.0±3.9	26.8±3.7	<0.001	0.89 (0.85–0.92)	<0.001
Diabetes mellitus	132 (24.1)	398 (27.7)	0.106		
Hypertension	239 (43.6)	689 (47.9)	0.086		
Hyperlipidemia	101 (18.4)	294 (20.5)	0.315		
HCV RNA >800,000 IU/mL	283 (51.6)	858 (59.8)	0.001	0.84 (0.64–1.10)	0.215
HCV genotype 3	1 (0.2)	27 (1.9)	0.004	0.21 (0.03–1.65)	0.137
AST, IU/L	67.2±54.0	61.3±51.5	0.030	1.00 (1.00–1.00)	0.956
ALT, IU/L	78.0±68.8	78.5±73.8	0.871		
rGT, IU/L	57.4±89.2	54.9±68.8	0.627		
Platelet count, x10^3/μL	185.4±75.1	198.3±70.9	0.001	1.00 (1.00–1.00)	0.903
Baseline triglyceride, mg/dL	103.8±51.6	118.8±72.1	<0.001	1.00 (0.99–1.00)	0.078
Baseline total cholesterol, mg/dL	175.5±38.9	175.1±37.1	0.840		
Baseline HDL-C, mg/dL	49.3±14.2	46.0±13.8	<0.001	1.01 (0.99–1.01)	0.537
Baseline LDL-C, mg/dL	101.8±29.8	105.0±31.8	0.083		
Baseline FPG, mg/dL	111.0±40.5	115.5±39.4	0.060		
Baseline HbA1c, %	6.0±1.2	6.2±1.3	0.012	0.98 (0.89–1.13)	0.961
CMRF number	2.3±1.4	2.7±1.3	<0.001	0.87 (0.75–1.01)	0.063
Pretreatment FIB-4 ≥3.25[a]	201 (36.8)	355 (25.0)	<0.001	1.92 (0.76–1.88)	0.449
Post-treatment FIB-4 ≥3.25[b]	118 (22.0)	165 (11.7)	<0.001	1.35 (0.85–2.14)	0.198
DAA regimen					
SOF+RBV	35 (6.4)	71 (4.9)	0.123		
LDV/SOF±RBV	78 (14.2)	197 (13.7)			
PrOD±RBV	75 (13.7)	185 (12.9)			
DCV/ASV	24 (4.4)	56 (3.9)			
EBR/GZR	59 (10.8)	109 (7.6)			
GLE/PIB	118 (21.5)	322 (22.4)			
SOF/VEL	139 (25.4)	446 (31.0)			
SOF/DCV	14 (2.5)	36 (2.5)			
SOF/VEL/VOX	4 (0.7)	15 (1.0)			
Others	2 (0.4)	1 (0.1)			

Variables are expressed as mean±standard deviation or number (%).
MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body Mass Index; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGT, r-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FIB-4, fibrosis-4 index; CMRF, cardiometabolic risk factor; DAA, directly acting antivirals; PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir; DCV, daclatasvir; ASV, asunaprevir; SOF, sofosbuvir; LDV, ledipasvir; EBR, elbasvir; GZR, grazoprevir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; VEL, velpatasvir; VOX, voxilaprevir.
[a]Data available in 1,968 patients. [b]Data available in 1,952 patients tested at 3 months after the end of treatment.

SLD, there was no significant status transition of MASLD as a whole after HCV eradication.

Recent regional recommendations have categorized SLD patients by judging their CMRFs, alcohol consumption and

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Table 5. Factors associated with MASLD development in baseline non-MASLD patients

Variables	MASLD (–)→(+) (n=595, 15.4%)	MASLD (–)→(–) (n=3,259, 84.6%)	*P*-value	Multivariate analysis	
				Odd ratio (95% CI)	*P*-value
Age, years	61.9±11.5	63.6±12.3	0.002	1.00 (0.99–1.01)	0.695
Sex, Male	274 (46.1)	1,441 (44.2)	0.408		
Baseline BMI, kg/m^2	25.4±3.8	23.7±3.7	<0.001	1.10 (1.06–1.14)	<0.001
Diabetes mellitus	158 (26.6)	700 (21.5)	0.006	0.96 (0.66–1.40)	0.827
Hypertension	261 (43.9)	1,308 (40.1)	0.089		
Hyperlipidemia	83 (14.0)	389 (11.9)	0.168		
HCV RNA >800,000 IU/mL	357 (60.0)	1,734 (53.3)	0.003	1.17 (0.90–1.51)	0.234
HCV genotype 3	5 (0.8)	45 (1.4)	0.284		
AST, IU/L	61.2±48.4	65.2±51.4	0.068		
ALT, IU/L	73.4±65.9	72.6±75.0	0.786		
rGT, IU/L	58.8±81.7	54.2±72.1	0.322		
CMRF number	2.3±1.2	1.7±1.4	<0.001	0.99 (0.86–1.14)	0.911
Platelet count, x10^3/μL	186.4±76.3	168.2±75.2	<0.001	1.002 (1.000–1.004)	0.102
Triglyceride, mg/dL	100.8±53.4	94.7±52.7	0.044	1.00 (1.00–1.00)	0.296
Total cholesterol, mg/dL	172.8±34.8	170.0±37.6	0.156		
HDL-C, mg/dL	47.9±14.7	50.9±16.1	0.001	1.00 (0.99–1.00)	0.332
LDL-C, mg/dL	101.2±29.5	96.7±31.0	0.009	1.00 (1.00–1.01)	0.027
FPG, mg/dL	110.5±36.1	108.1±33.1	0.213		
HbA1c, %	6.0±1.3	5.8±1.0	0.001	1.19 (1.04–1.35)	0.010
Pretreatment FIB-4 ≥3.25[a]	193 (32.6)	1,419 (43.7)	<0.001	1.06 (0.72–1.55)	0.776
Post-treatment FIB-4 ≥3.25[b]	120 (20.4)	968 (30.2)	<0.001	0.74 (0.49–1.12)	0.152
DAA regimen					
SOF+RBV	37 (6.2)	172 (5.3)	0.492		
LDV/SOF±RBV	84 (14.1)	472 (14.5)			
PrOD±RBV	90 (15.1)	504 (15.5)			
DCV/ASV	39 (6.6)	144 (4.4)			
EBR/GZR	59 (9.9)	312 (9.6)			
GLE/PIB	113 (19.0)	679 (20.8)			
SOF/VEL	149 (25.0)	851 (26.1)			
SOF/DCV	15 (2.5)	93 (2.8)			
SOF/VEL/VOX	7 (1.2)	24 (0.7)			
Others	2 (0.4)	8 (0.3)			

Variables are expressed as mean±standard deviation or number (%).
MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGT, r-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; FIB-4, fibrosis-4 index; CMRF, cardiometabolic risk factor; DAA, directly acting antivirals; PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir; DCV, daclatasvir; ASV, asunaprevir; SOF, sofosbuvir; LDV, ledipasvir; EBR, elbasvir; GZR, grazoprevir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; VEL, velpatasvir; VOX, voxilaprevir.
[a]Data available in 3,849 patients. [b]Data available in 3,796 patients tested at 3 months after the end of treatment.

etiologies.[9,10] The direct steatogenic nature of the HCV GT3 viral protein may lead to a specific cause of SLD in CHC patients.[16] The proportion of HCV GT3 was extremely low in the population, and there was no difference in the HCV-

3 distribution between patients with and without SLD. Meanwhile, the SLD was largely attributed to the metabolic disorders. We have recently shown an increased risk of cardiovascular and fibrotic risk in SLD patients with CMRFs in CHC, and it is rational to incorporate CHC patients with SLD and CMRFs as MASLD.[11] HCV is known to utilize host lipid droplets as a scaffold for viral assembly. HCV core protein inhibits the activity of microsomal triacylglycerol transfer protein (MTP), which is an essential and rate-limiting factor in the assembly and secretion of very low-density lipoprotein (VLDL-C), resulting in liver steatosis and hypolipidemia.[17] In addition, lipoproteins play an important role in the process of HCV infection since complexing of the virus to VLDL-C or LDL-C could promote endocytosis of HCV via the LDL receptor.[18] Therefore, HCV infection commonly leads to blood lipid changes and resulting liver steatosis.

HCV eradication improves insulin resistance, mitigates beta-cell function and further facilitates glycemic control.[6,8,19] Moreover, the release of entrapped lipoproteins from the liver after HCV eradication reverses hypolipidemia. We also observed a decrease in glycemic indices and an increase in lipid profiles after achieving SVR as in previous studies. Although an increase in LDL-C after viral clearance may be linked to certain vascular events,[7] HCV eradication ameliorates atherosclerosis[8,20] and decreases the risk of cardiovascular disease in the long run.[21] However, despite the favorable changes in glucose and HDL-C levels, a subtle change in BMI and an unfavorable change in LDL-C and triglyceride levels, we did not observe a significant change in terms of the status of CMRF carriage before and after viral eradication according to the regional recommendations. It raises the issue that the criteria of each CMRF were defined based on a certain cutoff value, and the all-or-none rule hardly reflects the actual alleviation or aggravation of metabolic risks. Furthermore, it may be easier to define “CMRF development” carriage because patients may only need to fulfill any one of 5 criteria than to define “CMRF resolution” carriage, as all five unfavorable factors need to be resolved no matter how many of them patients originally had. Last, the core determinant of cerebrovascular diseases, LDL-C, was not viewed as one of the CMRFs. Future studies on non-liver-related outcomes in CHC patients should be interpreted with caution.

Hepatic steatosis has been associated with poor liver-related outcomes in CHC patients.[4] Either pretreatment[22,23] or posttreatment[24] hepatic steatosis has been reported to increase the risk for the development of liver cirrhosis and hepatocellular carcinoma after antiviral treatment. Unlike in HCV-3 infection, in which hepatic steatosis can be ameliorated after viral clearance, whether the status of SLD would be augmented after achieving SVR is elusive. In the present study, we did not observe a significant trend toward an increase or decrease in the proportion of hepatic steatosis after HCV clearance. The emergence of liver steatosis has been observed following viral clearance, irrespective of body weight changes.[25-27] Nevertheless, other studies have shown a reduction in hepatic steatosis after achieving SVR, regardless of viral genotype.[28-30] Therefore, this issue remains an area of debate.[8] The discrepant results across studies may be attributed to heterogeneous metabolic characteristics, different definitions of hepatic steatosis and variable follow-up periods after SVR.

With the emerging terminology and definition, we were able to explore this issue by evaluating the shifts in the SLD and CMRF status collectively. Although both newly developed and resolved MASLD occurred in a proportion of subjects, the modification as a whole was not significant after HCV eradication. Notably, we observed that BMI and certain metabolic profiles were associated with MASLD development or resolution. These results are in line with reports that a high BMI and poor baseline metabolic profiles, such as HbA1c and LDL-C levels, are unfavorable factors for hepatic steatosis resolution or development after HCV eradication.[26,30,31]

The current study had several limitations. The posttreatment evaluation period may not be long enough to truly reflect the postviral status of the CMRFs and SLD. Even though we tried to enroll as many patients as we can, selection bias may exist by excluding patients without hepatic steatosis information. To our knowledge, this is the first nationwide study to explore this issue using the new definition of MASLD in the CHC cohort. Subjects were recruited from clinics, regional hospitals to medical centers, which might be representative of Taiwanese patients. In conclusion, HCV eradication mitigates MASLD in CHC patients. CMRF surveillance is mandatory for CHC patients with metabolic alterations, which are altered after HCV eradication, and can be used to predict the evolution of MASLD. Further studies are warranted to address the long-term hepatic and cardiovascular outcomes for patients who have altered

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MASLD status in the post-viral eradication era.

Authors' contribution

Conception and design: Ming-Lung Yu and Jee-Fu Huang. Acquisition of data: Chung-Feng Huang, Po-Cheng Liang, Pei-Chien Tsai, Yu-Ju Wei, Chih-Wen Wang, Tyng-Yuan Jang, Ming-Lun Yeh, Ming-Yen Hsieh, Yi-Hung Lin, Chao-Kuan Huang, Chia-Yen Dai, Wan-Long Chuang, Jee-Fu Huang, and Ming-Lung Yu. Data analysis and interpretation: Chung-Feng Huang, Tzu-Chun Lin and Ming-Lung Yu. Manuscript drafting and critical revision: Chung-Feng Huang, Jee-Fu Huang and Ming-Lung Yu. Approval of the final version of the manuscript: Jee-Fu Huang and Ming-Lung Yu.

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Conflicts of Interest

Ming-Lung Yu: Research support (grant) from BMS, Gilead, Merck and Roche diagnostics. Consultant of Abbvie, BMS, Gilead, Roche and Roche diagnostics. Speaker of Abbvie, BMS, Eisai, Gilead, Roche and Roche diagnostics.

Chung-Feng Huang: Speaker for AbbVie, BMS, Gilead, Merck, and Roche.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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