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Cure or curd: Modification of lipid profiles and cardio-cerebrovascular events after hepatitis C virus eradication

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Abstract

Hepatitis C virus (HCV) eradication deteriorates lipid profiles. Although HCV eradication may reduce the risk of vascular events as a whole, whether deteriorated lipid profiles increases the risk of cardio-cerebral disease in certain patients is elusive. Serial lipid profiles were measured before, during, at and 3 months after the end of direct-acting antivirals (DAAs) therapy, and annually thereafter in chronic hepatitis C patients who achieved a sustained virological response (SVR, undetectable HCV RNA at posttreatment week 12). The primary end-point was the occurrence of the events. A total of 617 patients were included, with a mean follow-up period of 26.8 months (range: 1-65 months). The total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels increased significantly from treatment week 4 to 2 years after treatment. Logistic regression analysis revealed that the factors independently associated with a significant cholesterol increase included age (odds ratio [OR]/95% confidence intervals [CIs]:1.02/1.006-1.039, P = .007) and smoking (OR/CI:3.21/1.14-9.02, P = .027). Five patients developed cardio-cerebral diseases during 1376 person-years follow-up period. Compared to patients without vascular events, a significantly higher

Abbreviations: CHC, chronic hepatitis C; DAA, direct-acting antiviral agents; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SVR, sustained virological response.; T-CHOL, total cholesterol.

proportion of those with vascular events experienced an LDL-C surge >40% (80% vs 19.9%, P = .001). Cox-regression analysis revealed that an LDL-C surge >40% was the only factor predictive of vascular events (HR/CI: 15.44/1.73-138.20, P = .014). Dyslipidemia occurred after HCV eradication, and it was associated with the risk of cardio-cerebrovascular diseases. Attention should also be paid to the extrahepatic consequence beyond liver-related complications in the post-SVR era.

KEYWORDS

CAD, DAA, HCV, lipid, SVR

1 | INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading etiologies of liver-related morbidities and mortalities worldwide. In addition, the lymphotropic and immune-mediated properties of HCV elicit a variety of extrahepatic presentations, including metabolic disarrangements. Due to the requirement for and interaction with lipoprotein and apolipoprotein in the HCV life cycle,[1,2] HCV infection is associated with low circulatory lipid profiles.[3,4] On the other hand, HCV eradication by interferon-based therapy reverses hypolipidemia,[5] and this results should also be found after therapy with direct-acting antivirals (DAAs).[6–8] Nevertheless, the results have not been consistent regarding certain lipid profiles across studies.[8–10]

From a clinical viewpoint, patients with chronic hepatitis C (CHC) are at a higher risk of cardio-cerebrovascular disease.[11,12] On the other hand, HCV eradication may reduce the risk of vascular events.[13–15] This finding is reciprocal to the emergence of dyslipidemia in the post-curative status. Indeed, not all of the studies supported the benefits of HCV eradication with regard to reducing the risk of coronary heart disease or stroke.[16] Notably, many of the previous studies addressing the changes of circulatory lipid profiles were limited to short-term follow-up after viral eradication. In addition, the linkage between the deterioration of the lipid profiles and the development of cardio-cerebrovascular disease has never been explored. In the current study, we aimed to address this issue by enrolling a characteristic CHC cohort with a clearly defined medical history of lipid-lowering agents and serial lipid profiles before and after DAA treatment. Meanwhile, each subject was monitored for lipid-lowering agent prescriptions and the development of cardio-cerebrovascular disease in the post-SVR status after DAA therapy.

2 | METHODS

CHC patients who received interferon-free oral DAA regimens were consecutively enrolled in a medical center and two regional hospitals from December 2015 to September 2018 in Taiwan. Patients were excluded if they did not achieve sustained virological response (SVR, defined as undetectable HCV RNA throughout 12 weeks of the posttreatment follow-up period [SVR12]). Lipid profiles including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured at 1 month before antiviral therapy, treatment week 4, the end of treatment, 3 months after the end of treatment, and annually thereafter. The patient history of dyslipidemia was ascertained, and the drug history regarding the prescription of lipid-lowering agents before, during, and after DAA therapy was also recorded. There was no specific intervention regarding diet or lifestyle modification of the CHC cohort throughout the treatment and follow-up period. The institutional review board of the Kaohsiung Medical University Hospital approved the protocols, which followed the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients provided written informed consent.

The primary end-point was the onset of cardio-cerebrovascular disease, defined as stable/unstable angina, acute myocardial infarction, ischemic, or hemorrhagic stroke. Patients with preexisting vascular events were excluded. HCV RNA and genotypes were measured using a real-time PCR assay (RealTime HCV; Abbott Molecular, Des Plaines, Illinois; detection limit: 12 IU/mL).[17] Liver cirrhosis was defined by liver histology,[18] transient elastography (FibroScan; Echosens, Paris, France; >12 kPa),[19] acoustic radiation force impulse (>1.98 m/s),[20] the fibrosis-4 index (>6.5)[21]; the presence of clinical, radiologic, endoscopic, or laboratory evidence of cirrhosis and/or portal hypertension; or symptoms of clinical hepatic decompensation (ascites, hepatic encephalopathy, jaundice, variceal hemorrhage). Dyslipidemia history was defined as (a) a history of any prescription for statins and (b) a total cholesterol level >200 mg/dL at no fewer than 2 measurement points or at least >1 report of a total cholesterol level >200 mg/dL plus an LDL-C level >130 mg/dL before allocation.

2.1 | Statistical analyses

Frequencies were compared between groups using the χ^2 test with the Yates correction or Fisher's exact test. Group means are presented as the means ± SD and were compared using analysis of variance and Student's t test or the nonparametric Mann-Whitney test. The fibrosis index 4 (FIB-4) was calculated by the following formula: age (years) × aspartate aminotransferase (AST) [U/L]/(platelets [10^9/L] × (alanine transaminase (ALT) [U/L]))$^{1/2}$. The change in lipid

profiles before and after DAA treatment was compared by a paired *t* test. Logistic regression analysis was performed to identify factors associated with a significant increase in the lipid profile, defined as a >50 % delta change in the total cholesterol level 3 months after the end of treatment. Stepwise multivariate linear regression was used to analyze which variables were correlated with the posttreatment cholesterol and LDL-C levels. Kaplan-Meier analysis and the log-rank test were performed to compare the differences in the occurrence of cardio-cerebrovascular disease between the determining factors. The risk factors independently associated with events were evaluated using Cox regression analysis by including variables with $P < .1$ in univariate analysis. The areas under the curve were generated from the receiver operating characteristic analysis were compared to determine the cutoff value for lipid profiles that could be used to predict the events. The procedures were performed using the SPSS 12.0 statistical package (SPSS Inc., Chicago, Illinois). All statistical analyses were based on two-sided hypothesis tests with a significance level of $P < .05$.

3 | RESULTS

A total of 617 patients were enrolled in the current study (mean age, 62.1 years; 42.3% male). The basic demographic, virological, and clinical features and DAA regimens of the patients are shown in Table 1. One hundred seven patients (17.3%) had a history of dyslipidemia. Of those, 42 (6.8%) patients did not receive lipid-lowering agents before DAA treatment, whereas 65 (10.5%) patients kept receiving lipid-lowering agents before and during the DAA treatment period (7 patients changed statins and 2 patients decreased their statin dosages due to potential drug-drug interactions).

3.1 | Serial changes in lipid profiles

The lipid profiles and medical records were monitored over a mean follow-up period of 26.8 months (range: 1-65 months) post-DAA treatment. Serial changes in lipid profiles among patients without concurrent lipid-lowering agents before DAA are shown in Figure 1 and Supplementary Table 1. Lipid levels including total cholesterol, triglycerides, HDL-C, and LDL-C increased gradually during and after DAA initiation compared to their pretreatment levels. Total cholesterol (from 169 ± 34 to 173 ± 37 mg/dL, $P = .002$) and LDL-C (from 95 ± 27 to 100 ± 30 mg/dL, $P < .001$) levels increased significantly sooner than the other lipid levels at treatment week 4. A significant increase in triglycerides was noted at/after the end of treatment (from 97 ± 50 to 105 ± 64 mg/dL, $P < .001$), whereas a significant increase in HDL-C was observed only at 12 weeks after the end of treatment (from 50 ± 15 to 53 ± 17 mg/dL, $P < .001$). The total cholesterol and LDL level increased up to 189 and 110 mg/dL, respectively, 12 weeks after the end of treatment. The levels of total cholesterol and LDL-C were steady after 1 year and remained significantly higher than the pretreatment levels throughout 2 years of follow-up.

TABLE 1 Characteristics of the chronic hepatitis C patients

	All patients (n = 617)
Age (years, mean [SD])	62.1 (11.0)
Male, n (%)	261 (42.3)
Body weight (kg, mean [SD])	64.4 (12.5)
BMI (kg/m^2, mean [SD])	25.2 (4.1)
AST (IU/L, mean [SD])	74.7 (55.1)
ALT (IU/L, mean [SD])	83.0 (63.1)
Hemoglobin (g/dL, mean [SD])	13.4 (1.8)
Platelet count (×10^3 U/L, mean [SD])	162 (72)
Total cholesterol (mg/dL, mean [SD])	170.7 (35.2)
Triglycerides (mg/dL, mean [SD])	99.9 (53.4)
HDL-C (mg/dL, mean [SD])	49.9 (15.5)
LDL-C (mg/dL, mean [SD])	95.6 (27.8)
HBsAg seropositivity, n (%)	40 (6.5)
HCV RNA (log IU/mL, mean [SD])	5.72 (0.94)
HCV RNA > 400 000 IU/mL, n (%)	394 (63.9)
HCV genotype 1, n (%)	493 (79.9)
Diabetes, n (%)	155 (25.1)
Hypertension, n (%)	235 (38.1)
Dyslipidemia history, n (%)	107 (17.3)
Without lipid lowering agents	42 (6.8)
With lipid lowering agents	65 (10.5)
HCC history, n (%)	83 (13.5)
Liver cirrhosis, n (%)	182 (29.5)
FIB-4 (mean [SD])	4.21 (3.76)
FIB-4 > 3.25, n (%)	306 (49.6)
DAA regimen, n (%)	
Daclatasvir/asunaprevir	47 (7.6)
PrOD ± ribavirin	307 (49.8)
Elbasvir/grazoprevir	18 (2.9)
Sofosbuvir/ledipasvir ± ribavirin	89 (14.4)
Sofosbuvir/ribavirin	57 (9.2)
Sofosbuvir/daclatasvir ± ribavirin	60 (9.7)
Others	16 (2.6)

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase. BMI, body mass index; DAA, directly acting antivirals; FIB-4: fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PrOD, paritaprevir/ritonavir/ombitasvir with dasabuvir.

3.2 | Factors associated with the increased total cholesterol level after HCV eradication

We further explored the change in the total cholesterol levels in different patient subgroups (Table 2). The total cholesterol level increased significantly in all subpopulations except for those who kept using lipid-lowering agents at the time of DAA treatment and those

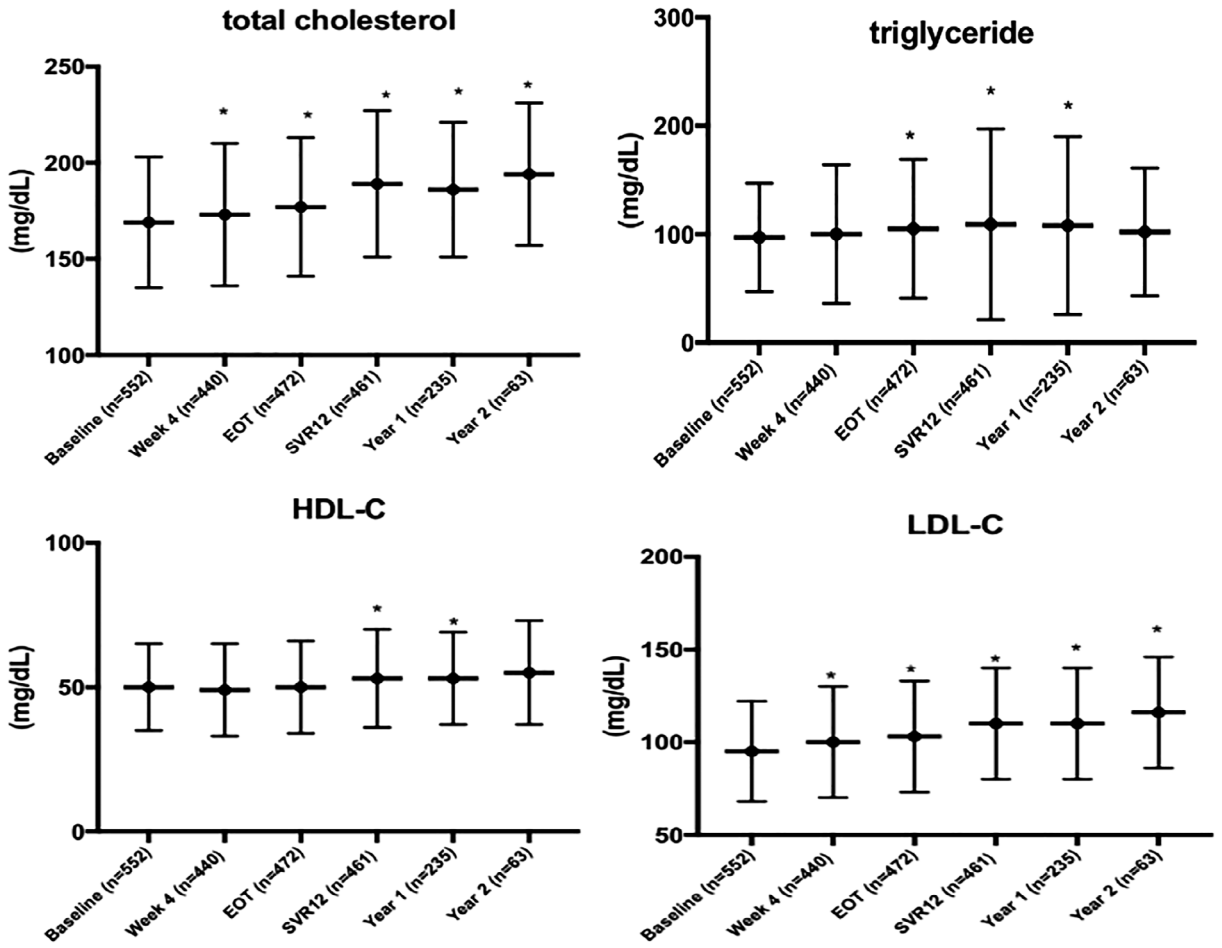

FIGURE 1 Serial changes in lipid profiles in patients not using lipid-lowering agents before antiviral therapy. Lipid profiles at year 1 and year 2 were calculated as the level at the time of lipid-lowering agent prescription if it occurred. *P < .05 compared with pretreatment level. EOT, end of treatment; SVR12, 12 weeks after end-of-treatment

who were coinfected with hepatitis B virus. Patients with a history of dyslipidemia who were not receiving treatment had the highest cholesterol levels both before and after DAA treatment, whereas patients with liver cirrhosis had the lowest cholesterol levels both before and after DAA treatment. We further addressed factors associated with significantly increased total cholesterol levels, defined as an increased total cholesterol level with a greater than 50 % change in the level of cholesterol, 15 mg/dL, among the 512 patients with available lipid profiles 3 months after the end of treatment. As shown in Table 3, elderly patients and patients who smoked were more likely to have a significant total cholesterol increase. Logistic regression analysis revealed that the factors independently associated with significant cholesterol increases included age (odds ratio [OR]/95% confidence intervals [CIs]: 1.02/1.006-1.039, P = .007) and smoking (OR/CI: 3.21/1.14-9.02, P = .027).

Linear regression analysis revealed that the factors correlated to high cholesterol levels 3 months after the end of treatment were a dyslipidemia history without treatment (β: 0.19; CI: 14.72, 40.13; P < .001), non-liver cirrhosis (β: −0.17; CI: −21.31, −6.81, P < .001) and female sex (β: −0.15; CI: −18.60, −6.99, P < .001), whereas the factors correlated to a high LDL-C level were a dyslipidemia history without treatment (β: 0.18; 95% CI: 10.43, 30.98; P < .001) and non-liver cirrhosis (β: −0.14; 95% CI: −15.32, −3.63, P = .002) (Table 4).

Forty-five (7.3%) patients without concurrent treatment with lipid-lowering agents at the time of DAA initiation were eventually treated with lipid-lowering agents during the follow-up period. Serial changes in the lipid profiles of the patients are shown in Supplementary Figure 1 and Supplementary Table 1. The mean values of total cholesterol, triglyceride, HDL-C and LDL-C were 233 mg/dL (range: 125-351 mg/dL), 184 mg/dL (range: 32-963 mg/dL), 52 mg/dL (range: 18-91 mg/dL), and 143 mg/dL (range: 36-230 mg/dL), respectively, at the time of lipid-lowering agent prescription.

3.3 | LDL-C surge and vascular events in the post-DAA follow-up period

Five patients developed vascular events during 1376 person-years follow-up period. Two patients developed cerebrovascular diseases, and the other three developed cardiovascular diseases. Patient

TABLE 2 Changes of total cholesterol level in patients with different subgroups

	Pre-treatment (mg/dL, mean [SD])	Post-treatment[a] (mg/dL, mean [SD])	Delta change (mg/dL, mean [SD])	*P* value
Gender				
Male	166 (35)	183 (37)	16 (28)	<.001
Female	175 (36)	193 (39)	18 (31)	<.001
Age, years				
<60	178 (37)	192 (41)	14 (28)	<.001
≥60	168 (34)	187 (37)	19 (31)	<.001
BMI, kg/m^2				
<24	171 (36)	190 (36)	19 (30)	<.001
≥24	171 (35)	188 (41)	17 (30)	<.001
Smoking				
No	172 (36)	189 (39)	17 (30)	<.001
Yes	160 (34)	192 (33)	32 (22)	<.001
Diabetes				
No	173 (36)	191 (38)	18 (27)	<.001
Yes	166 (34)	183 (41)	17 (38)	<.001
Hypertension				
No	172 (35)	191 (38)	18 (28)	<.001
Yes	170 (36)	186 (40)	16 (32)	<.001
Dyslipidemia history				
No	167 (32)	186 (37)	19 (27)	<.001
Yes, non-treated	200 (39)	217 (38)	16 (35)	.008
Yes, treated	183 (46)	190 (46)	7 (42)	.21
HCV genotype				
1	170 (35)	187 (38)	17 (30)	<.001
Non-1	177 (39)	194 (40)	17 (28)	<.001
HCV viral loads				
<400 000 IU/mL	167 (35)	187 (38)	20 (30)	<.001
≥400 000 IU/mL	174 (36)	190 (39)	16 (30)	<.001
HBsAg				
Negative	171 (36)	189 (39)	18 (30)	<.001
Positive	175 (36)	182 (35)	7 (34)	.30
HCC history				
No	173 (36)	190 (39)	17 (30)	<.001
Yes	164 (33)	181 (37)	17 (29)	<.001
Liver cirrhosis				
No	176 (37)	193 (39)	17 (32)	<.001
Yes	161 (31)	180 (37)	18 (26)	<.001
FIB-4				
<3.25	178 (37)	194 (38)	16 (31)	<.001
≥3.25	164 (33)	184 (39)	19 (29)	<.001

Note: Data were expressed as mean (SD).

Abbreviations: BMI, body mass index; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; FIB-4, fibrosis-4 index.

[a]3 months after end-of-treatment.

characteristics, including the potential risk factors and serial changes in their lipid profiles, are shown in Supplementary Table 2. All five patients had normal lipid profiles before DAA treatment and developed progressive dyslipidemia after achieving SVR and before developing vascular events. Meanwhile, the glucose status was stable throughout the course. Four patients were treated with statin

TABLE 3 Factors associated with significant increased total cholesterol after achieving SVR

	No significant increase (n = 254)	Significant increase (n = 258)	*P* value	Logistic regression analysis		
				OR	95% CI	*P* value
Age (years, mean [SD])	60.6 (11.3)	63.2 (10.6)	.008	1.02	1.006-1.039	.007
Male, n (%)	105 (41.3)	106 (41.1)	.95			
BMI (kg/m^2, mean [SD])	25.5 (4.4)	24.9 (3.9)	.11			
Smoking, n (%)	5 (2.0)	15 (5.8)	.025	3.21	1.14-9.02	.027
Diabetes, n (%)	65 (25.6)	61 (23.6)	.61			
Hypertension, n (%)	99 (39.0)	99 (38.4)	.89			
AST (IU/L, mean [SD])	71.3 (52.5)	78.0 (47.9)	.13			
ALT (IU/L, mean [SD])	78.3 (64.3)	88.3 (62.0)	.07			
HCV RNA ≥ 400 000 IU/mL, n (%)	168 (66.1)	156 (60.5)	.18			
HCV genotype 1, n (%)	209 (82.3)	203 (78.7)	.30			
HBsAg (+), n (%)	16 (6.3)	12 (4.7)	.41			
Liver cirrhosis	77 (30.3)	80 (31.0)	.87			
HCC, n (%)	32 (12.6)	36 (14.0)	.65			
FIB-4 ≥ 3.25, n (%)	121 (47.6)	129 (50.0)	.59			

Note: significant increased total cholesterol: >50% of delta change of cholesterol, 15 mg/dL, 3 months after end-of-treatment.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence intervals; FIB-4, fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; OR, odds ratio; SVR, sustained virological response.

TABLE 4 Factors correlated to high total cholesterol and LDL-C level after achieving sustained virological response*

	B	SE	95% confidence interval for B		Beta	*P* value
Total cholesterol						
Dyslipidemia history	27.42	6.47	14.72	40.13	0.19	<.001
Liver cirrhosis	−14.06	3.69	−21.31	−6.81	−0.17	<.001
Male	−11.79	3.46	−18.60	−4.99	−0.15	.001
LDL-C						
Dyslipidemia history	20.70	5.23	10.43	30.98	0.18	<.001
Liver cirrhosis	−9.47	2.97	−15.32	−3.63	−0.14	.002

Note: * data were measured 3 months after end of treatment. Variables including age, sex, body mass index, diabetes, hypertension, smoking, HCV genotype, HCV viral loads (<400 000 vs ≥400 000 IU/mL), liver cirrhosis, hepatitis B virus dual infection and dyslipidemia history (no dyslipidemia/dyslipidemia with drug control [reference] vs dyslipidemia without drug control).
Abbreviation: LDL-C, low-density lipoprotein cholesterol.

whereas the other one was prescribed fibrate at the time of developing vascular events. As shown in Table 5, patients with vascular events had lower pretreatment HDL-C levels, higher posttreatment total cholesterol/HDL-C ratios and substantially greater LDL-C increase ratio. A Cox hazard regression model revealed that the increase in the LDL-C level was associated with the development of the events (hazard ratio [HR]/CI: 4.81/1.10-20.97, *P* = .037). The best cutoff value of the LDL-C increase ratio for predicting the vascular events was 1.47 (AUROC 0.65, *P* = .09). We further used an LDL-C surge >40% (LDL-C increase ratio 1.4) as the cutoff value. One hundred two (20.5%) of the 498 patients experienced an LDL-C surge after initiating DAA therapy. A significantly higher proportion of patients with vascular events had an LDL-C surge than those without (80% [4/5] vs 19.9% [98/493], *P* = .007). The 1-, 2-, and 3-year cumulative incidence of cardio-cerebrovascular disease events were 1.0%, 9.3%, and 16.7%, respectively, among patients with an LDL-C surge after DAA therapy, compared to 0.3%, 0.5%, and 1.3%, respectively, among those without an LDL-C surge after DAA therapy (log-rank test *P* = .001; Supplementary Figure 2). Cox regression analysis revealed that an LDL-C surge >40% after DAA therapy was the only factor predictive of the vascular events (HR/CI: 15.44/1.73-138.20, *P* = .014).

TABLE 5 Factors associated with cardio-cerebrovascular disease occurrence after achieving sustained virological response

				Cox regression analysis		
	CCD (–)	CCD (+)	*P* value	HR	95% CI	*P* value
Age (years, mean[SD])	62.1 (11.1)	68.2 (6.5)	.10	1.06	0.97-1.16	0.19
Male, n (%)	257 (42.0)	4 (80.0)	.17			
BMI (kg/m^2, mean [SD])	25.2 (4.1)	24.6 (2.4)	.61			
Smoking, n (%)	24 (3.9)	1 (20.0)	.19			
Diabetes, n (%)	154 (25.2)	1 (20.0)	1			
Hypertension, n (%)	233 (38.1)	2 (40.0)	1			
Dyslipidemia history, n (%)	42 (6.9)	0 (0)	1			
AST (IU/L, mean [SD])	74.8 (50.3)	62.4 (16.5)	.17			
ALT (IU/L, mean [SD])	83.0 (63.2)	79.2 (47.6)	.87			
Pretreatment TC (mg/dL, mean [SD])	170.9 (35.2)	147.8 (24.7)	.10	0.99	0.96-1.03	.74
Pretreatment TG (mg/dL, mean [SD])	99.7 (53.2)	128.2 (73.5)	.44			
Pretreatment HDL-C (mg/dL, mean [SD])	50.1 (15.6)	37.6 (7.8)	.02	0.94	0.86-1.02	.13
Pretreatment LDL-C (mg/dL, mean [SD])	95.7 (27.8)	81.2 (25.3)	.27			
Pretreatment LDL-C/TC ratio mean (SD)	0.56 (0.94)	0.54 (0.08)	.68			
Pretreatment TC/HDL-C ratio, mean (SD)	3.66 (1.13)	4.06 (0.98)	.41			
Pretreatment TG/HDL-C ratio, mean (SD)	2.31 (1.92)	3.84 (3.03)	.32			
Post-treatment TC (mg/dL, mean [SD])	188.7 (38.6)	189.0 (41.1)	.99			
Post-treatment TG (mg/dL, mean [SD])	111.0 (86.5)	172.4 (105.6)	.26			
Post-treatment HDL-C (mg/dL, mean [SD])	53.2 (16.9)	40.9 (14.9)	.14			
Post-treatment LDL-C (mg/dL, mean [SD])	110.1 (30.8)	120.9 (51.7)	.67			
Post-treatment LDL-C/TC ratio, mean (SD)	0.58 (0.09)	0.61 (0.19)	.45			
Post-treatment TC/HDL-C ratio, mean (SD)	3.84 (1.28)	4.86 (1.13)	.05	1.04	0.44-2.50	.93
Post-treatment TG/HDL-C ratio, mean (SD)	2.56 (2.56)	5.29 (4.46)	.24			
TC increment ratio, mean (SD)	1.12 (0.19)	1.29 (0.30)	.14			
LDL-C increment ratio, mean (SD)	1.19 (0.31)	1.50 (0.64)	.09	4.81	1.10-20.97	.037
HCV genotype 1, n (%)	490 (80.1)	3 (60.0)	.26			
HCV RNA > 400 000 IU/mL, n (%)	391 (63.9)	3 (60.0)	1			
HBsAg (+), n (%)	40 (6.5)	0 (0)	1			
FIB-4	4.2 (3.8)	3.2 (1.2)	.14			
HCC, n (%)	83 (13.6)	0 (0)	1			

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCD, cardio-cerebrovascular disease; CI, confidence intervals; FIB-4, fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

4 | DISCUSSION

In the current study, we demonstrated that lipid profiles were augmented after HCV eradication. Lipidemic components, in particular total cholesterol and LDL-C, increased sooner after DAA initiation and HCV suppression. The levels increased progressively after the end of treatment and remained elevated consistently with a mean 15% and 22% increase in total cholesterol and LDL-C levels, respectively, after more than 2 years of follow-up. Certain patients were eventually prescribed lipid-lowering agents at the physicians' discretion, and in the majority, this may be considered to be a risk reduction strategy of cardio-cerebrovascular disease.[22] Nevertheless, vascular events occurred in a subset of patients who experienced progressively deteriorating lipid profiles. We found that an LDL-C surge >40% was the only predictor and may serve as a warning sign for potential vascular events after HCV eradication in this population.

We have previously demonstrated that HCV viremia is a factor affecting lower serum lipid levels either in a hospital-based cohort[3] or from large community surveillance data.[4] HCV eradication by antiviral therapy can reverse the course. Possible mechanisms include the release of entrapped intrahepatic lipids, modulation of the genes responsible for lipid metabolism,[23] and the modification of the LDL regulator protein convertase subtilisin/kexin 9 (PCSK9).[24] The reversal of lipid levels after HCV eradication has been well addressed in the

interferon era.[5] An increasing number of reports have also addressed this issue in the DAA era.[8] A more consistent finding has been documented regarding the increase in total cholesterol and LDL-C levels after HCV eradication; however, the increases in the levels of HDL-C and TG are still controversial. Some studies observed parallel increases in the two parameters, similar to that observer for total cholesterol and LDL-C, whereas other studies found inverse or nonsignificant changes in the two parameters.[8] Notably, the majority of the studies compared the change only before and soon after anti-HCV treatment, and reports regarding the dynamic changes during DAA treatment and a longer follow-up period are scarce. In the current study with a relatively large sample size, we observed that the increases in the levels of the four lipid components were universal, but the rate and extent of those increases after viral suppression varied among different parameters. Total cholesterol and LDL-C increased sooner after the initiation of DAAs, whereas TG and HDL-C increased slowly after the end of therapy. This was in line with the finding that quickly elevated total cholesterol and LDL-C levels may correlate with rapid viral clearance due to therapy with potent DAAs.[25] Moreover, we identified that the elevation of the lipid levels was not transient but rather persisted years after the end of therapy. Notably, age and smoking were factors associated with pronounced lipid changes after viral eradication. Patients with a history of dyslipidemia without treatment had high lipid levels in the post-SVR status. All of the factors mentioned above were also risk factors for cardio/cerebral-vascular events.

Different thresholds (from 70, 100, 155, to 190 mg/dL) and goals for LDL-C reduction have been advised to reduce the risk of atherosclerotic cardiovascular disease (ASCVD), which mainly depends on the initial LDL-C level, age, ethnicity, and foreseeable cardiovascular disease incidence by risk estimation.[26] The current evidence regarding managing patients with dyslipidemia seems to favor the concept "lower is better."[22] Due to the lower lipid profiles before anti-HCV therapy, deteriorating lipid profiles are frequently overlooked in the post-SVR era; 7.3% of the patients without concurrent treatment with lipid-lowering agents before antivirals started taking lipid-lowering agents during the follow-up period. After excluding patients who took lipid-lowering agents both before and after anti-HCV therapy, the proportion of patients with LDL >100 mg/dL increased from 37.5% before treatment to 56.9% after anti-HCV therapy, whereas the proportion of patients with LDL levels >155 mg/dL increased from 2% before treatment to 7.2% after antiviral therapy (data not shown). A significantly increased proportion of patients warranted lipid-lowering agents to reduce the risk of vascular events in the post-SVR era. However, lipid-lowering treatment may be greatly underutilized in this special population.[27]

HCV eradication has been suggested to reduce cardio-cerebral vascular risk compared to viremic status.[13,14] In a recent study, 731 of the 17 103 treated patients who achieved SVR experienced cardiovascular events during the follow-up period (19.1 per 1000 person-years). A 13% risk reduction was observed in CHC patients receiving interferon- or DAA-based regimens compared to the untreated cohort.[13] Nevertheless, another large cohort study comprising 160 875 subjects revealed that the benefit of HCV eradication was only found with regard to reducing the risk of stroke but not coronary heart disease compared to the untreated cohort.[16] We may take a closer look at the new events and their associations with the underlying risk factors, including the changes in lipid profiles. Notably, two of the five patients who experienced cardio-cerebrovascular disease after anti-HCV therapy had no obvious risk factors for cardio-cerebrovascular disease before antiviral therapy. One commonality was that most of them had progressively deteriorating lipid profiles with lipid level surges after HCV eradication, and the LDL-C surge was the only independent predictor of an event. LDL-C rebound after the discontinuation of statin therapy following an attack of acute myocardial infarction (AMI) increased the post-AMI mortality rate.[28] Viremic CHC patients should be viewed as a high-risk population for the vascular events, [11,12] and their pretreatment lower lipid levels should be considered pseudomorphic. Whether the dramatically increased lipid levels after HCV eradication simulates the LDL rebound in the post-MI status needs further exploration. DAAs have been shown to improve carotid thickening, but carotid plaques did not change in the same cohort.[29] Meanwhile, a recent study has shown dyslipidemia and a short-term increase in aortic stiffness among patients with advanced fibrosis after DAA treatment.[30] Taken collectively, the amelioration of vascular events in the post-SVR status should be judged on an individual basis while taking the lipid dynamics into account.

The current study was limited by relatively short follow-up period, and there were no uninfected or viremic controls. The number of patients with the vascular events might also be limited to draw a definite conclusion in the current study. However, the incidence rate of the events up to 5 years of follow-up was similar to what has been reported in the other cohort,[13] and we clearly depicted the risk factors and serial change of the lipid profiles until the occurrence of the vascular events in the index cases. In conclusion, dyslipidemia occurs after HCV eradication. A post-SVR LDL-C surge was associated with the risk of the vascular events. Current guidelines advocating post-SVR follow-up strategies mainly focus on the risk of hepatocellular carcinoma development. Patients without advanced liver disease are recommended to be discharged without the need for further follow-up.[31,32] Attention should still be paid to the extrahepatic consequence, cardio-cerebrovascular disease, and not just the liver-related complications in the post-SVR era. As LDL-C supplies the main driving force for cardiovascular events,[26] whether the increase in LDL-C levels is offset by the reduction in systemic inflammation in SVR patients with regard to cardio-cerebrovascular disease development should be investigated in future research.

CONFLICT OF INTEREST

All authors declared no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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