Association of serum lipid profile with liver fibrosis in HCV-coinfected HIV patients on suppressive anti-retroviral therapy

SOMKID SRISOPA[1,2], DUANGNATE PIPATSATITPONG[3] and CHAREEPORN AKEKAWATCHAI[3,4]

[1]Graduate Program in Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Pathumthani 12121, Thailand; [2]Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi 11000, Thailand; [3]Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Pathumthai 12121, Thailand; [4]Thammasat University Research Unit in Diagnostic Molecular Biology of Chronic Diseases related to Cancer (DMB-CDC), Pathumthani 12121, Thailand

Received March 3, 2024; Accepted July 24, 2024

DOI: 10.3892/br.2024.1834

Abstract. Hepatitis C virus (HCV) coinfection in individuals living with human immunodeficiency virus (HIV) (PLWH) may affect lipid metabolism and accelerate the progression of chronic hepatitis. Therefore, the identification of risk factors for progressive liver disease is needed. The present study aimed to examine the prevalence and clinical features associated with liver fibrosis in HCV-coinfected HIV patients, including metabolic markers. A total of 105 patients coinfected with HIV and HCV were recruited and liver fibrosis was assessed using the fibrosis-4 (FIB-4) score and aspartate aminotransferase-to-platelet ratio index (APRI). Logistic regression analyses indicated that patients aged >50 years and with a $CD4^+$ cell count <350 cells/μl had an 11.4-times higher (P=0.001) and a 5.7-times higher (P=0.017) risk of liver fibrosis, as determined by FIB-4 score, compared to patients aged ≤40 years and a $CD4^+$ cell count of ≥350 cells/μl, respectively. In addition, patients naïve to HCV treatment or receiving treatment had 5.4- and 12.7-times higher risks for liver fibrosis, as determined by APRI, than those with sustained virologic response (SVR) (P=0.003 and P=0.033, respectively). Univariate analysis indicated lower risks of liver fibrosis, as determined by APRI, in the patients with abnormally high levels of cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) than those with normal levels [odds ratio (OR) 0.3, 95% confidence interval (CI) 0.1-0.9, P=0.037; OR 0.4, 95% CI 0.2-0.9, P=0.041; OR 0.2, 95% CI 0.1-0.5, P=0.001] and multivariate analysis suggested only patients with high levels of LDL had a lower risk for liver fibrosis determined by APRI (OR 0.1, 95% CI 0.3-0.8, P=0.029). Consistently, serum levels of cholesterol, HDL and LDL were significantly lower in the patient groups with more advanced fibrosis, evaluated by FIB-4 score and APRI, than those without liver fibrosis and the levels of cholesterol and LDL in the patients achieving SVR were higher than those with no response or not receiving treatment (all P<0.05). In conclusion, the present study identified serum lipid levels as associated factors of hepatic fibrosis, together with age, $CD4^+$ cell count and HCV treatment status, in HCV-coinfected PLWH on long-term suppressive anti-retroviral therapy.

Correspondence to: Dr Chareeporn Akekawatchai, Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Rungsit campus, 99 Moo 18 Piyachart Building, Paholyotin Road, Pathumthani 12121, Thailand
E-mail: cakekawatchai@gmail.com, ejareepo@tu.ac.th

Key words: hepatitis C virus, human immunodeficiency virus, liver fibrosis, lipid profiles

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease in individuals living with human immunodeficiency virus (HIV) (PLWH) under anti-retroviral therapy (ART) (1,2) due to shared common routes of transmission. Worldwide, ~2.3 million individuals are estimated to be coinfected with HIV and HCV (2). A cohort study of the Asia HIV observational database reported ≤15.2% of HCV coinfection in HIV-infected individuals (3) and studies in Thai PLWH have also suggested a high prevalence of 4-11% (4-7). This coinfection causes a higher risk of progressive hepatitis and accelerates the progression to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (1,2,8). HIV infection causes hepatitis C-mediated liver fibrosis by direct and indirect mechanisms. HIV directly activates hepatocytes, hepatic stellate cells and Kupffer cells, which cooperatively participate in inflammation and fibrogenesis in the liver. HIV infection also causes microbial translocation, indirectly inducing liver injury, impaired HCV immune responses and fibrogenesis (2). While studies support the pathological effects of coinfection in both HIV- and HCV-mediated disease progression, advancements in the management of HIV-infected patients with ART in the past decade (1,2) and the use of direct-acting antivirals (DAAs) for chronic HCV infection adds more complexity to the treatment and care of chronic liver disease caused by HIV and HCV coinfection.

Previous studies have indicated significant liver fibrosis and multiple risk factors for the severity and progression of liver diseases in PLWH, including age, sex, $CD4^+$ cell count, $CD4^+/CD8^+$ ratio, HIV RNA levels, alcohol consumption, diabetes mellitus and HCV coinfection (4,9-11). Although studies in HCV-infected patients have demonstrated various clinical conditions associated with liver fibrosis and progression to HCC either before or after the DAA era, such as age, duration of infection, diabetes mellitus and alcohol consumption (12,13), the progression of chronic hepatitis C in PLWH may be more advanced and complicated (14). Moreover, studies have indicated glucose and lipid abnormalities associated with commonly used anti-retroviral (ARV) drug regimens in PLWH (15,16). However, disordered glucose and lipid metabolism in HCV-coinfected patients with HIV under ART remains to be elucidated. The present study aimed to examine the prevalence and associated clinical features of liver fibrosis in Thai patients coinfected with HIV and HCV under suppressive ART. In particular, metabolic markers in this patient group were determined. The present study provided data supporting the development of diagnosis, treatment and care for HCV-coinfected PLWH.

Materials and methods

Study population, clinical data and laboratory investigation. A retrospective cross-sectional study was conducted on 105 patients coinfected with HIV and HCV attending Bamrasnaradura Infectious Diseases Institute (Thailand) between November 2016 and December 2017. As shown in Fig. 1, the patients were aged >20 years, with documented HIV and HCV infection and blood samples and clinical data were available (Table I). Patients with documented hepatitis B virus (HBV) infection, active opportunistic infections (OIs) and who regularly consumed alcohol, herbal medicine, paracetamol and steroid medications were excluded from the study. All subjects provided written informed consent. The study protocol was reviewed and approved by the Human Ethics Committee No. 3, Thammasat University (approval no. 070/2560) and the Bamrasnaradura Infectious Diseases Institute (approval no. R005/60). The patients were previously characterized and the distribution and clinical significance of HCV genotypes in the present study group were reported in a previous study (17).

Clinical data and laboratory investigation. Data collected from the medical records of the patients included age, sex, HIV infection diagnosis, duration of HIV infection, currently used ARV drugs, duration of ART, duration of HCV infection, HCV and HBV infection diagnosis, pretreatment HCV viral load, HCV genotypes, current HCV treatment status and OIs. Data collected from a screening questionnaire included weight, height, alcohol consumption, steroid and paracetamol drug intake and herbal medicine use. All patients underwent clinical examination and blood samples were subjected to testing for HIV viral load (Roche Molecular Diagnostics); $CD4^+$ cell count (BD Biosciences); platelet count (Beckman Coulter, Inc.); liver function tests, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Roche Diagnostics); fasting blood sugar (FBS); and serum lipid levels, including cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride (TG) (Roche Diagnostics).

Sustained virologic response (SVR) was defined as negative HCV RNA at 6 months after completing HCV treatment (18). Liver fibrosis was evaluated by fibrosis score-4 (FIB-4), which was classified into class 1 (≤1.45), class 2 (1.46-3.25) and class 3 (>3.25) (19,20) and AST-to-platelet ratio index (APRI), which was classified into class 1 (≤0.5), class 2 (0.51-1.5) and class 3 (>1.5) (21). Abnormal levels of FBS were defined as ≤110 mg/dl (22-24). According to the National Cholesterol Education Program, Adult Treatment Panel III guidelines (24), lipid profile abnormalities included hypercholesterolemia, defined as cholesterol levels ≥200 mg/dl; hypertriglyceridemia, defined as TG levels ≥150 mg/dl; high LDL cholesterol, defined as ≥130 mg/dl; and low HDL cholesterol, defined as <40 mg/dl in men and <50 mg/dl in women (24). Metabolic markers, including TG/HDL ratio and TG-glucose index, were also determined to predict cardiometabolic disease. In the present study, the cut-off values of TG/HDL ratio were 2.6 for men and 1.7 for women, while those of TG-glucose index were 9.2 (25,26).

Statistical analysis. Data are presented as the mean ± standard derivation, median (range) and percentages. The χ^2 and Fisher's exact tests were used to determine the association between categorical variables and liver fibrosis, as assessed by FIB-4 score and APRI, whereas the Mann-Whitney U test was used to analyze the association between liver fibrosis or HCV therapy and continuous variables. The level of statistical significance was set at $P<0.05$. Univariate and multivariate logistic regression was performed to determine the risks for liver fibrosis. Odds ratio (OR) with 95% confidence interval (CI) values and P-values were calculated. $P<0.05$ was considered to indicate a statistically significant difference. The statistical analysis was performed using SPSS version 15.0 (SPSS Inc.).

Results

The present study was conducted on 105 patients with HIV and HCV coinfection according to the flow diagram in Fig. 1. The study consisted of 95 (90.5%) male and 10 (9.5%) female patients, with median ages of 46 (27-67) years and 47 (34-61) years, respectively. The mean $CD4^+$ cell count was 566±2.66 cells/ml and 91% (93/102) of patients had undetectable levels of HIV viral load (<20 copies/ml). The majority of patients (99/100) were on ART, 78% (78/100) on 2 nucleoside reverse transcriptase inhibitors (2NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), 7% (7/100) on 2NRTIs and protease inhibitors (PIs). and 15% (15/100) on other antiretroviral drugs. Only 1% (1/100) of the patients were naïve to ART. The median duration of ART was 9 (2-20) years. In this patient group (Table I), the prevalence of patients coinfected with HCV genotypes 1, 3 and 6 were 54.8% (40/73), 37% (27/73) and 8.2% (6/73), respectively and 90.1% (64/71) of the patients had pretreatment HCV viral load >5.0 log IU/ml (17). A total of 51% (51/100) of the patients were on HCV therapy with 35% (35/100) achieving SVR, 7% (7/100) not achieving SVR and 9% (9/100) currently receiving treatment. The prevalence of patients having significant liver fibrosis assessed by

Table I. Characteristics of Thai patients coinfected with HIV and HCV according to the presence of significant liver fibrosis assessed by FIB-4 score and APRI (n=105).

Characteristic	All n (%)	FIB-4			APRI		
		≤1.45	>1.45	P-value	≤0.5	>0.5	P-value
All patients	105	49 (46.7)	56 (53.3)	-	38 (36.2)	67 (63.8)	-
Sex							
M	95 (90.5)	46 (48.4)	49 (51.6)		35 (36.8)	60 (63.2)	
F	10 (9.5)	3 (30.0)	7 (70.0)	0.331[a]	3 (30.0)	7 (70.0)	0.745[a]
Age, years							
≤40	25 (23.8)	16 (64.0)	9 (36.0)		8 (32.0)	17 (68.0)	
41-50	48 (45.7)	25 (52.1)	23 (47.9)		18 (37.5)	30 (62.5)	
>50	32 (30.5)	8 (25.0)	24 (75.0)	0.008[b]	12 (37.5)	20 (62.5)	0.883
$CD4^+$ cell count, cells/μl (n=102)							
≥350	87 (85.3)	45 (51.7)	42 (48.3)		34 (39.1)	53 (60.9)	
<350	15 (14.7)	3 (20.0)	12 (80.0)	0.027[a,b]	3 (20.0)	12 (80.0)	0.245
Antiretroviral therapy (n=100)							
Others	15 (15.0)	6 (40.0)	9 (60.0)		4 (26.7)	11 (73.3)	
2NRTIs and NNRTI	78 (78.0)	40 (51.3)	38 (48.7)	0.144	30 (38.5)	48 (61.5)	0.650
2NRTIs and PI	7 (7.0)	1 (14.3)	6 (85.7)		3 (42.9)	4 (57.1)	
HCV genotypes (n=73)							
G1	40 (54.8)	20 (50.0)	20 (50.0)		15 (37.5)	25 (62.5)	
G3	27 (37.0)	10 (37.0)	17 (63.0)		9 (33.3)	18 (66.7)	
G6	6 (8.2)	2 (33.3)	4 (66.7)	0.498	3 (50.0)	3 (50.0)	0.743
Pretreatment HCV viral load, log IU/ml (n=71)							
<5.00	7 (9.9)	3 (42.9)	4 (57.1)		3 (42.9)	4 (57.1)	
≥5.00	64 (90.1)	25 (39.1)	39 (60.9)	1.000[a]	19 (29.7)	45 (70.3)	0.669[a]
SVR to HCV therapy (n=100)							
SVR	35 (35.0)	21 (60.0)	14 (40.0)		23 (65.7)	12 (34.3)	
Non-SVR	7 (7.0)	3 (42.9)	4 (57.1)		2 (28.6)	5 (71.4)	
Naïve to treatment	49 (49.0)	21 (42.9)	28 (51.1)	0.173	10 (20.4)	39 (79.6)	<0.001[b]
On treatment	9 (9.0)	2 (22.2)	7 (77.8)		1 (11.1)	8 (88.9)	
FBS, mg/dl (n=104)							
<110	80 (76.9)	38 (47.5)	42 (52.5)		29 (36.2)	51 (63.8)	
≥110	24 (23.1)	11 (45.8)	13 (54.2)	1.000[a]	9 (37.5)	15 (62.5)	1.000[a]
Cholesterol, mg/dl (n=100)							
<200	83 (83.0)	37 (44.6)	46 (55.4)		26 (31.3)	57 (68.7)	
≥200	17 (17.0)	10 (58.8)	7 (41.2)	0.301[a]	10 (58.8)	7 (41.2)	0.050[a]
HDL, mg/dl (n=99)							
M <40, F <50	36 (36.4)	15 (41.7)	21 (58.3)		9 (25.0)	27 (75.0)	
M ≥40, F ≥50	63 (63.6)	33 (52.4)	30 (47.6)	0.403[a]	29 (46.0)	34 (54.0)	0.053[a]
LDL, mg/dl (n=101)							
<130	78 (77.2)	35 (44.9)	43 (55.1)		22 (28.2)	56 (71.8)	
≥130	23 (22.8)	13 (56.5)	10 (43.5)	0.352[a]	16 (69.6)	7 (30.4)	0.001[a,b]
TG, mg/dl (n=102)							
<150	68 (66.7)	30 (44.1)	38 (55.9)		21 (30.9)	47 (69.1)	
≥150	34 (33.3)	17 (50.0)	17 (50.0)	0.674[a]	15 (44.1)	19 (55.9)	0.196[a]
TG/HDL ratio (n=96)							
M <2.6, F <1.7	45 (46.9))	20 (44.4)	25 (55.6)		15 (33.3)	30 (66.7)	
M ≥2.6, F ≥1.7	51 (53.1)	26 (51.0)	25 (49.0)	0.522	21 (41.2)	30 (58.8)	0.428

Table I. Continued.

Characteristic	All n (%)	FIB-4 ≤1.45	FIB-4 >1.45	P-value	APRI ≤0.5	APRI >0.5	P-value
TG-glucose index (n=101)							
<9.2	100 (100)	47 (46.5)	54 (53.5)		36 (35.6)	65 (64.4)	
≥9.2	0 (0)	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND

[a]Fisher's exact test; [b]P<0.05. HIV, human immunodeficiency virus; HCV, hepatitis C virus; FIB-4, fibrosis-4; APRI, aspartate aminotransferase-to-platelet ratio index; M, male; F, female; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SVR, sustained virologic response; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; M, male; F, female.

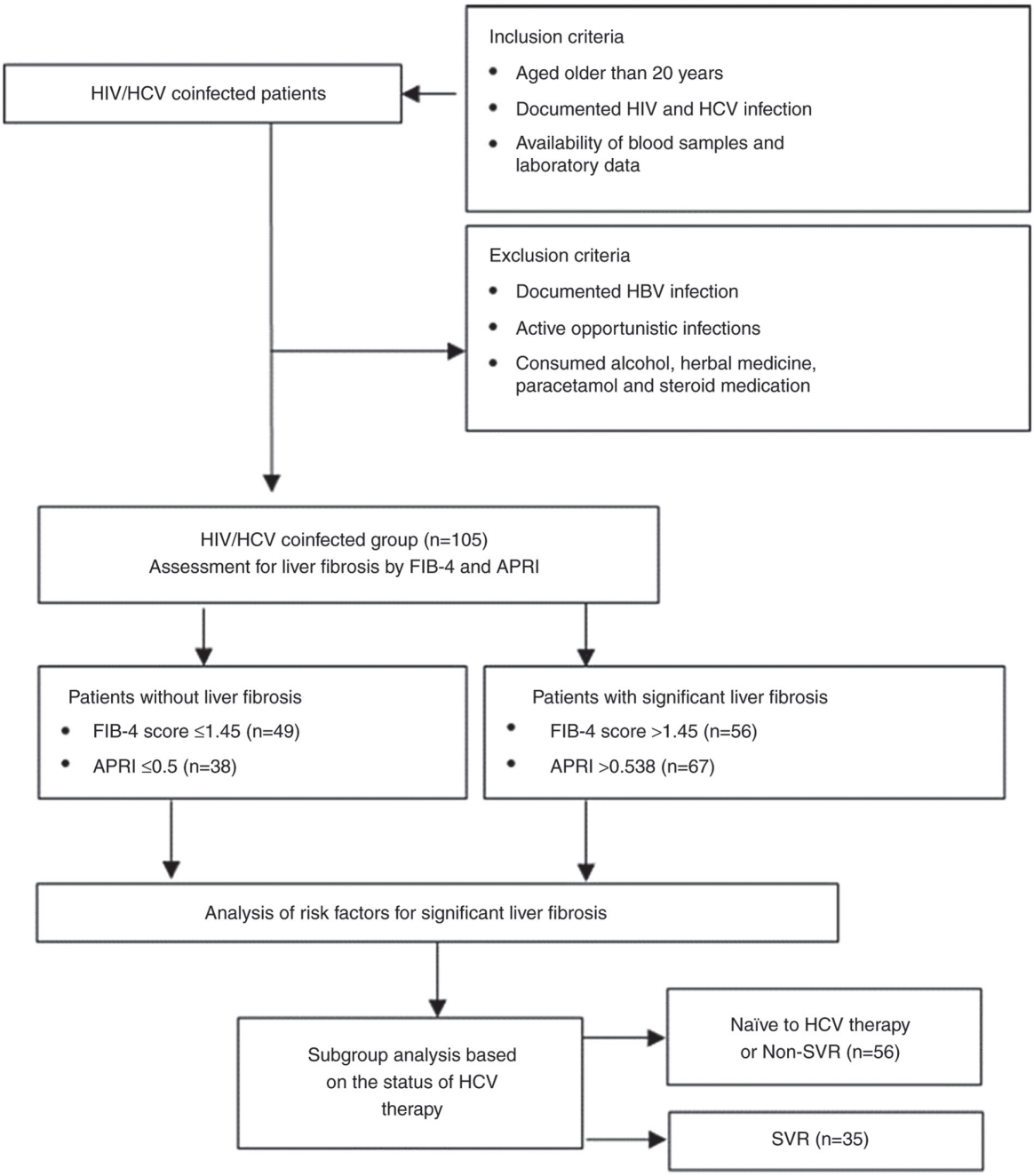

Figure 1. Flow diagram showing the design of the present study. HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; FIB-4, fibrosis-4; APRI, aspartate aminotransferase-to-platelet ratio index; SVR, sustained virologic response.

FIB-4 scores >1.45 was 53.3% and by APRI >0.5 was 63.8%. The rates of patients with abnormal levels of FBS were 23.1% (24/104), whereas those with hypercholesterolemia, hypertriglyceridemia, high LDL and low HDL cholesterol were 17% (17/100), 33.3% (34/102), 22.8% (23/101) and 36.4% (36/99), respectively. In the present study group, the median values of metabolic markers, TG/HDL ratio and TG-glucose index, were 2.62 (0.48-23.94) and 4.69 (4.3-5.66) respectively. The rates of patients at risk for cardiometabolic diseases with a TG/HDL ratio >2.6 for men and 1.7 for women were 53.1% (51/96). However, no patients with a TG-glucose index >9.2 were observed.

The characteristics of the patients according to the presence of significant liver fibrosis are shown in Table I. The majority of characteristics of the patients with and without significant liver fibrosis, as evaluated by FIB-4 score and APRI, were similar. However, age and $CD4^+$ cell count were significantly associated with liver fibrosis, as assessed by FIB-4 scores (P=0.008 and P=0.027, respectively); and HCV treatment status, cholesterol and LDL levels were associated with liver fibrosis, as assessed by APRI (P<0.001, P=0.050 and P=0.001, respectively). The data were consistent with the univariate and multivariate analyses of risk factors for significant liver fibrosis in the present study group (Table II). Multivariate analysis indicated that patients aged >50 years had an 11.4 times higher risk (P=0.001) and those with a $CD4^+$ cell count <350 cells/μl had a 5.7 times higher risk (P=0.017) for liver fibrosis, as assessed by FIB-4 scores, than those aged ≤40 years and with a $CD4^+$ cell count ≥350 cells/μl respectively. Univariate and multivariate analyses indicated that patients naïve to HCV treatment had 7.5 times (P=0.001) and 5.4 times (P=0.003) higher risks than those with SVR, respectively. Similarly, patients who were on HCV treatment had 15.3 times (P=0.015) and 12.7 times (P=0.033) higher risks than patients with SVR, respectively. Notably, the univariate analysis indicated that patients developing hypercholesterolemia, high HDL and high LDL cholesterol had lower risks than those with normal levels (OR 0.3, 95% CI 0.1-0.9, P=0.037; OR 0.4, 95% CI 0.2-0.9, P=0.041; OR 0.2, 95% CI 0.1-0.5, P=0.001, respectively). However, only patients with high LDL cholesterol remained at a lower risk (OR 0.1, 95% CI 0.3-0.8, P=0.029) according to multivariate analysis adjusted for sex, age, $CD4^+$ cell count, ARV treatment, HCV genotypes, pretreatment HCV viral load, HCV treatment, FBS and a lipid panel.

Analysis by the Mann-Whitney U test, shown in Table III, indicated significantly higher levels of AST in patients with moderate and advanced liver fibrosis, as assessed by FIB-4 scores (P=0.004 and P<0.001, respectively) and APRI (both P<0.001) and higher levels of ALT were detected in patients with moderate and advanced liver fibrosis, as assessed by APRI (both P<0.001), than those without fibrosis. Patients with moderate and advanced fibrosis evaluated by FIB-4 scores were significantly older than those without liver fibrosis (P<0.031 and P<0.001, respectively). Consistent with the univariate and multivariate analyses, considerably lower levels of cholesterol, HDL and LDL were observed in the patients with advanced liver fibrosis, with a FIB-4 score >3.25 and APRI >1.5 (all P<0.05).

As univariate and multivariate analyses indicated a significant association of HCV treatment status with liver fibrosis evaluated by APRI, laboratory parameters, including lipid profiles, age, $CD4^+$ cell count and liver enzymes stratified by HCV treatment status were analyzed by the Mann-Whitney U test (Table IV). The data showed that there was no significant difference between the median ages and $CD4^+$ cell counts in the SVR and with naïve to HCV treatment or non-SVR patient groups. The SVR group had significantly higher median levels of liver enzymes, AST and ALT and liver fibrosis, as determined by FIB-4 and APRI, than those in the naïve to HCV treatment or non-SVR patient groups (P<0.001, P<0.001, P=0.047 and P<0.001, respectively), indicating that the therapy achieving SVR had improved liver pathology. Consistent with the lower levels of lipids, cholesterol, HDL and LDL observed in the patients with advanced liver fibrosis, median levels of cholesterol and LDL in patients in the naïve to treatment or non-SVR groups were significantly lower than those observed in the SVR group (P=0.031 and P=0.039, respectively). These data may suggest an involvement of lipid metabolism in liver fibrosis in patients with HIV and HCV coinfection.

Discussion

HCV coinfection is well-established as a major risk for the progression of chronic liver disease in PLWH (1,2,10,27). The present study was conducted on Thai patients coinfected with HIV and HCV mostly on long-term suppressive ART. A total of 51% of the present study group underwent HCV therapy with an SVR rate of 35%. The data indicated the high prevalence of patients developing significant liver fibrosis and the relatively high rates of those with abnormally high levels of FBS, lipid profiles, which were total cholesterol, TG, LDL and HDL and TG/HDL in the present study group. Previous studies have indicated that, in the era of ART, HCV/HIV coinfection accelerates the progression of hepatitis to advanced chronic liver disease and HCC and can cause higher liver-related mortality (8,14,28,29). Moreover, the commonly used ARV drugs in PLWH are associated with impaired FBS and abnormal lipid profiles, contributing to increasing risks for diabetes and cardiovascular disease (15,16). Thus, the present study group has the potential to develop advanced liver disease and metabolic disorders. However, metabolic alterations in PLWH who are coinfected with HCV appear to be more complicated. In the present study, clinical features associated with significant liver fibrosis, particularly metabolic profiles, in patients coinfected with HIV and HCV mostly on suppressive ART were investigated.

Similar to previous studies on HCV- or HIV-infected patients (4,10,12,13), clinical features associated with significant liver fibrosis in this HCV and HIV-coinfected patient group were identified. While patients aged >50 years and with a $CD4^+$ cell count <350 cells/μl exhibited a high risk for significant liver fibrosis, as assessed by FIB-4 scores, patients naïve to or receiving HCV treatment carried a high risk for liver fibrosis, as determined by APRI. Notably, the analysis also indicated a significant association of lipid levels with liver fibrosis evaluated by APRI. Patients who developed hypercholesterolemia, high HDL and high LDL levels had lower risks for liver fibrosis than those with normal levels, which was consistent with the significant reduction of lipid levels in more advanced liver fibrosis observed in the patients with FIB-4 scores >3.25 and APRI >1.5 compared with those without liver fibrosis. In addition, the data indicated that HCV

Table II. Univariate and multivariate analyses of risks for liver fibrosis in Thai patients coinfected with HIV and HCV (n=105).

Characteristic	Enrolled patients N (%)	Patients with FIB-4 >1.45	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Patients with APRI >0.5	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Sex											
M	95 (90.5)	49 (87.5)	1				60 (89.6)	1			
F	10 (9.5)	7 (12.5)	2.2 (0.5-9.0)	0.276			7 (10.4)	1.4 (0.3-5.6)	0.669		
Age, years											
≤40	25 (23.8)	9 (16.0)	1		1		17 (25.4)	1			
41-50	48 (45.7)	23 (41.1)	1.6 (0.6-4.4)	0.332	2.5 (0.7-8.0)	0.123	30 (44.7)	0.8 (0.3-2.2)	0.642		
>50	32 (30.5)	24 (42.9)	5.3 (1.7-16.7)	0.004[a]	11.4 (2.8-47.0)	0.001[a]	20 (29.9)	0.8 (0.3-2.4)	0.666		
$CD4^+$ cell count, cells/μl (n=102)											
≥350	87 (85.3)	42 (77.8)	1		1		53 (81.5)	1			
<350	15 (14.7)	12 (22.2)	4.3 (1.1-16.3)	0.032[a]	5.7 (1.4-24.1)	0.017[a]	12 (18.5)	2.6 (0.7-9.8)	0.167		
ARV drugs (n=100)											
Others	15 (15.0)	9 (17.0)	1				11 (17.5)	1			
2NRTIs and NNRTI	78 (78.0)	38 (71.7)	0.6 (0.2-2.0)	0.426			48 (76.2)	0.6 (0.2-2.0)	0.389		
2NRTIs and PI	7 (7.0)	6 (11.3)	4 (0.4-42.2)	0.249			4 (6.3)	0.5 (0.1-3.2)	0.451		
HCV genotypes (n=73)											
G1	40 (54.8)	20 (48.8)	1				25 (54.4)	1			
G3	27 (37.0)	17 (41.4)	1.7 (0.6-4.6)	0.297			18 (39.1)	1.2 (0.4-3.3)	0.727		
G6	6 (8.2)	4 (9.8)	2.0 (0.3-12.2)	0.452			3 (6.5)	0.6 (0.1-3.4)	0.561		
Pretreatment HCV viral load, log IU/ml (n=71)											
<5.00	7 (9.9)	4 (9.3)	1				4 (8.2)	1			
≥5.00	64 (90.1)	39 (90.7)	1.2 (0.2-5.7)	0.845			45 (91.8)	1.8 (0.4-8.7)	0.479		
SVR to HCV therapy (n=100)											
SVR	35 (35.0)	14 (26.4)	1				12 (18.8)	1		1	
Non-SVR	7 (7.0)	4 (7.6)	2.0 (0.4-10.3)				5 (7.8)	4.8 (0.8-28.5)	0.085	3.2 (0.4-28.2)	0.297
Naïve to treatment	49 (49.0)	28 (52.8)	2.0 (0.8-4.8)				39 (60.9)	7.5 (2.8-20.0)	0.001[a]	5.4 (1.7-16.7)	0.003[a]
On treatment	9 (9.0)	7 (13.2)	5.3 (0.9-29.1)	0.057			8 (12.5)	15.3 (1.7-137.4)	0.015[a]	12.7 (1.2-131.9)	0.033[a]

Table II. Continued.

Characteristic	Enrolled patients N (%)	Patients with FIB-4 >1.45	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Patients with APRI >0.5	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
FBS, mg/dl (n=104)											
<110	80 (76.9)	42 (76.4)	1				51 (77.3)	1			
≥110	24 (23.1)	13 (23.6)	1.1 (0.4-2.7)	0.886			15 (22.7)	0.9 (0.4-2.4)	0.911		
Cholesterol, mg/dl (n=100)											
<200	83 (83.0)	46 (86.8)	1				57 (89.1)	1		1	
≥200	17 (17.0)	7 (13.2)	0.6 (0.2-1.6)	0.287			7 (10.9)	0.3 (0.1-0.9)	0.037[a]	2.0 (0.3-13.4)	0.489
HDL, mg/dl (n=99)											
M <40, F <50	36 (36.4)	21 (41.2)	1				27 (44.3)	1		1	
M ≥40, F ≥50	63 (63.6)	30 (58.8)	0.6 (0.3-1.5)	0.306			34 (55.7)	0.4 (0.2-0.9)	0.041[a]	0.5 (0.1-1.7)	0.269
LDL, mg/dl (n=101)											
<130	78 (77.2)	43 (81.1)	1				56 (88.9)	1		1	
≥130	23 (22.8)	10 (18.9)	0.6 (0.2-1.6)	0.328			7 (11.1)	0.2 (0.1-0.5)	0.001[a]	0.1 (0.3-0.8)	0.029[a]
TG, mg/dl (n=102)											
<150	68 (66.7)	38 (69.1)	1				47 (71.2)	1		1	
≥150	34 (33.3)	17 (30.9)	0.8 (0.3-1.8)	0.575			19 (28.8)	0.6 (0.2-1.3)	0.189	0.3 (0.1-1.1)	0.082

[a]P<0.05. Data were adjusted for sex, age, $CD4^+$ cell count, ARV treatment, HCV genotypes, pretreatment HCV viral load, HCV treatment, FBS and lipid profile in univariate and multivariate regression analyses. HIV, human immunodeficiency virus; HCV, hepatitis C virus; FIB-4, fibrosis-4; OR, odds ratio; CI, confidence interval; M, male; F, female; ARV, anti-retroviral; APRI, aspartate aminotransferase-to-platelet ratio index; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SVR, sustained virologic response; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table III. Median levels of lipid profiles, age, CD4+ cell count and liver enzymes stratified by FIB-4 scores and APRI in Thai patients coinfected with HIV and HCV.

	FIB-4 score					APRI				
Laboratory parameter	≤1.45 (n=49)	1.46-3.25 (n=35)	P-value	>3.25 (n=21)	P-value	≤0.5 (n=38)	0.51-1.5 (n=41)	P-value	>1.5 (n=26)	P-value
Age, years (n=105)	43.0 (27-65)	47.0 (36-67)	0.031[a]	55.0 (39-63)	<0.001[b]	45.0 (29-65)	44.0 (32-67)	0.423	48.0 (27-63)	0.345
CD4+ cell count, cells/μl (n=102)	534.5 (218-1,748)	507.5 (92-991)	0.477	470.0 (5-828)	0.066	529.0 (218-1,748)	559.5 (92-1,114)	0.717	477.0 (5-824)	0.147
AST, U/l (n=105)	37.0 (17-189)	57.0 (27-189)	0.004[a]	82.0 (48-420)	<0.001[b]	27.5 (17-64)	57.0 (31-115)	<0.001[b]	98.5 (48-420)	<0.001[b]
ALT, U/l (n=105)	42.0 (14-436)	52.0 (11-264)	0.583	62.0 (21-235)	0.139	28.0 (11-138)	65.0 (12-188)	<0.001[b]	97.5 (21-436)	<0.001[b]
FBS, mg/dl (n=104)	96.0 (67-128)	101.0 (84-160)	0.140	102.5 (81-146)	0.056	96.5 (84-126)	99.0 (82-160)	0.599	99 (67-157)	0.339
Cholesterol, mg/dl (n=100)	180.0 (102-242)	173.0 (113-267)	0.182	140.5 (82-205)	<0.001[b]	183.0 (102-267)	173.5 (113-235)	0.121	151.0 (82-205)	<0.001[b]
HDL, mg/dl (n=99)	45.0 (27-99)	51.0 (22-114)	0.419	35.0 (11-79)	0.009[a]	46.5 (28-99)	51.0 (22-114)	0.742	40.0 (11-79)	0.017[a]
LDL, mg/dl (n=101)	120.5 (67-174)	106.0 (69-188)	0.257	94.0 (37-153)	0.006[a]	123.5 (79-188)	117.0 (67-182)	0.570	91.0 (37-134)	<0.001[b]
TG, mg/dl (n=102)	126.0 (67-447)	108.0 (54-419)	0.138	136.0 (56-383)	0.433	127.5 (64-349)	112.5 (54-447)	0.310	130.0 (56-419)	0.285

Data are shown as median (range). [a]P<0.05 and [b]P<0.001. Some variables had missing data and n is given in parentheses. FIB-4, fibrosis-4; APRI, aspartate aminotransferase-to-platelet ratio index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

Table IV. Median levels of lipid profiles, age, CD4+ cell count, liver enzymes and liver fibrosis markers stratified by status of HCV therapy in patients coinfected with HIV and HCV.

Laboratory parameter	SVR (n=35)	Naïve to therapy or non-SVR (n=56)	P-value
Age, years (n=91)	48.0 (37.0-65.0)	45.0 (27.0-67.0)	0.062
CD4+ cell count, cells/μl (n=91)	530.0 (190.0-1,288.0)	551.0 (5.0-1,748.0)	0.365
AST, U/l (n=91)	31.0 (17.0-109.0)	67.0 (20.0-189.0)	<0.001[b]
ALT, U/l (n=91)	33.0 (11.0-138.0)	75.0 (12.0-436.0)	<0.001[b]
FIB-4 score (n=91)	1.2 (0.5-4.8)	1.6 (0.0-13.9)	0.047[a]
APRI (n=91)	0.4 (0.1-2.4)	1.0 (0.1-4.3)	<0.001[b]
Cholesterol, mg/dl (n=86)	179.0 (131.0-242.0)	171.0 (82.0-235.0)	0.031[a]
HDL, mg/dl (n=85)	52.0 (27.0-79.0)	45.0 (11.0-114.0)	0.177
LDL, mg/dl (n=87)	118.0 (75.0-188.0)	106.0 (37.0-182.0)	0.039[a]
TG, mg/dl (n=88)	120.0 (64.0-447.0)	118.0 (54.0-442.0)	0.985

Data shown as median (range). [a]P<0.05 and [b]P<0.001. Some variables had missing data and n is given in parentheses. HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FIB-4, fibrosis-4; APRI, AST-to-platelet ratio index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

treatment achieving SVR significantly increased the levels of lipids, cholesterol and LDL, in this HIV/HCV patient group. This was similar to the findings of previous studies indicating lower serum levels of total cholesterol, LDL, HDL and TG in HCV-monoinfected patients compared with those in negative subjects (30,31). The previous epidemiological study indicated

that HCV infection might cause hypolipidemia regardless of host factors, including age, nutrition and hepatic damage (31). The involvement of hypolipidemia with the outcome of liver transplantation has also been demonstrated in a patient group with high rates of HCV infection (32). Therefore, the association of lipid levels with liver fibrosis in HCV-coinfected PLWH observed in the present study was possibly due to HCV coinfection and the status of HCV treatment.

Initially, the present study observed the relatively high prevalence of patients at risk for cardiometabolic diseases, as indicated by lipid profile abnormalities and TG/HDL ratio, which was consistent with a previous study in PLWH (16). However, the present data indicated no association between the abnormally high TG/HDL ratio and significant liver fibrosis as evaluated by FIB-4 and APRI. In addition, the logistic regression analysis indicated a negative association of lipid levels, cholesterol, HDL and LDL, with liver fibrosis as assessed by APRI. Indeed, HCV infection is closely associated with host lipid metabolism (33). Serum lipids serve roles in HCV virion circulation and entry into hepatocytes (33). The virus also employs different types of lipids to facilitate virion production and assembly (33). The inverse relationship between lipid levels and liver fibrosis observed in the present study may reflect the disruption of lipid metabolism caused by hepatic damage during HCV infection. While it has been reported that commonly used ARV drug regimens cause an increase in serum lipid levels in PLWH (16), the mechanisms underlying HCV infection-mediated host lipid metabolism in PLWH on suppressive ART require further clarification.

The limitations of the present study include that it contained a limited number of subjects, which may affect the statistical significance of the variables tested. Clinical data were obtained from retrospective medical reviews and the drug regimens used for hepatitis C therapy were unavailable. However, as the data collection was performed at a time when HCV therapy in Thailand was performed based on the clinical practice guidelines for the management of chronic hepatitis C 2015, all treated HCV-infected patients were likely to have received a combination of pegylated interferon and ribavirin (34). Thus, the present study provides data before the use of DAA therapy in Thailand.

In conclusion, the present cross-sectional study detected the high prevalence of liver fibrosis in HCV-coinfected PLWH, evaluated by non-invasive markers, FIB-4 scores and APRI. The analysis indicated that age, $CD4^+$ cell count, HCV treatment and lipid profiles, including cholesterol, HDL and LDL, were significantly associated with liver fibrosis. Notably, the reduction of serum lipid levels was significantly associated with the severity of chronic liver disease. Long-term monitoring for clinical outcomes related to lipid metabolism, particularly in patients starting DAA therapy, is warranted.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Thailand Science Research and Innovation Fundamental Fund fiscal year 2022 (grant no. 2493097) and the Thammasat University Research Unit in Diagnostic Molecular Biology of Chronic Diseases related to Cancer (DMB-CDC). Somkid Srisopa is a recipient of the Research Grant for Graduate Studies from the National Research Council of Thailand (fiscal year 2018, contract no. 7/2561).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CA contributed to funding acquisition, resources, supervision, study design, data analysis, manuscript preparation, review and editing. SS performed experimental work, data collection and analysis and manuscript preparation. DP contributed to the statistical analysis. SS and CA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol of the present study was reviewed and approved by the Human Ethics Committee no. 3, Thammasat University (approval no. 070/2560) and Bamrasnaradura Infectious Diseases Institute (approval no. R005/60), Thailand.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ganesan M, Poluektova LY, Kharbanda KK and Osna NA: Human immunodeficiency virus and hepatotropic viruses co-morbidities as the inducers of liver injury progression. World J Gastroenterol 25: 398-410, 2019.
2. Gobran ST, Ancuta P and Shoukry NH: A Tale of Two Viruses: Immunological Insights Into HCV/HIV Coinfection. Front Immunol 12: 726419, 2021.
3. Chen M, Wong WW, Law MG, Kiertiburanakul S, Yunihastuti E, Merati TP, Lim PL, Chaiwarith R, Phanuphak P, Lee MP, *et al*: Hepatitis B and C Co-Infection in HIV Patients from the TREAT Asia HIV observational database: Analysis of risk factors and survival. PLoS One 11: e0150512, 2016.
4. Akekawatchai C, Sretapunya W, Pipatsatitpong D and Chuenchit T: Hepatitis B or C virus coinfection in and risks for transaminitis in human immunodeficiency virus-infected Thais on combined antiretroviral therapy. Asian Biomedicine 9: 353-361, 2015.
5. Law WP, Dore GJ, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, Lange JM, Phanuphak P and Cooper DA: Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. AIDS 17: 2191-2199, 2003.
6. Sungkanuparph S, Wongprasit P, Manosuthi W and Atamasirikul K: Compliance with hepatitis B and hepatitis C virus infection screening among HIV-1 infected patients in a resource-limited setting. Southeast Asian J Trop Med Public Health 39: 863-866, 2008.

7. Thitipatarakorn S, Chinbunchorn T, Peelay J, Seekaew P, Amatavete S, Sangsai M, Pankam T, Avihingsanon A, Avery M, Phanuphak P, *et al*: Prevalence and the associated factors of hepatitis B and hepatitis C viral infections among HIV-positive individuals in same-day antiretroviral therapy initiation program in Bangkok, Thailand. BMC Public Health 22: 144, 2022.
8. Sun J, Althoff KN, Jing Y, Horberg MA, Buchacz K, Gill MJ, Justice AC, Rabkin CS, Goedert JJ, Sigel K, *et al*: Trends in hepatocellular carcinoma incidence and risk among persons with HIV in the US and Canada, 1996-2015. JAMA Netw Open 4: e2037512, 2021.
9. DallaPiazza M, Amorosa VK, Localio R, Kostman JR and Lo Re V III: Prevalence and risk factors for significant liver fibrosis among HIV-monoinfected patients. BMC Infect Dis 10: 116, 2010.
10. Chiraunyanann T, Changsri K, Sretapunya W, Yuenyongchaiwat K and Akekawatchai C: CXCL12 G801A polymorphism is associated with significant liver fibrosis in HIV-infected Thais: A cross-sectional study. Asian Pac J Allergy Immunol 37: 162-170, 2019.
11. Androutsakos T, Schina M, Pouliakis A, Kontos A, Sipsas N and Hatzis G: Causative factors of liver fibrosis in HIV-infected patients. A single center study. BMC Gastroenterol 20: 91, 2020.
12. de Torres M and Poynard T: Risk factors for liver fibrosis progression in patients with chronic hepatitis C. Ann Hepatol 2: 5-11, 2003.
13. Luna-Cuadros MA, Chen HW, Hanif H, Ali MJ, Khan MM and Lau DT: Risk of hepatocellular carcinoma after hepatitis C virus cure. World J Gastroenterol 28: 96-107, 2022.
14. Nguyen Truong T, Laureillard D, Lacombe K, Duong Thi H, Pham Thi Hanh P, Truong Thi Xuan L, Chu Thi N, Luong Que A, Vu Hai V, Nagot N, *et al*: High Proportion of HIV-HCV coinfected patients with advanced liver fibrosis requiring hepatitis C Treatment in Haiphong, Northern Vietnam (ANRS 12262). PLoS One 11: e0153744, 2016.
15. Tadesse WT, Adankie BT, Shibeshi W, Amogne W, Aklillu E and Engidawork E: Prevalence and predictors of glucose metabolism disorders among People Living with HIV on combination antiretroviral therapy. PLoS One 17: e0262604, 2022.
16. Waters DD and Hsue PY: Lipid abnormalities in persons living with HIV infection. Can J Cardiol 35: 249-259, 2019.
17. Somkid Srisopa DP and Chaereeporn Akekawatchai: Genotypic distribution of hepatitis C virus in human immunodeficiency virus-infected patients in Bamrasnaradura Infectious Diseases Institute. Journal of the Medical Technologist Association of Thailand 48: 7215-7226, 2020.
18. Cloherty G, Talal A, Coller K, Steinhart C, Hackett J Jr, Dawson G, Rockstroh J and Feld J: Role of serologic and molecular diagnostic assays in identification and management of hepatitis C virus infection. J Clin Microbiol 54: 265-273, 2016.
19. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, *et al*: Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 43: 1317-1325, 2006.
20. Foca E, Fabbiani M, Prosperi M, Quiros Roldan E, Castelli F, Maggiolo F, Di Filippo E, Di Giambenedetto S, Gagliardini R, Saracino A, *et al*: Liver fibrosis progression and clinical outcomes are intertwined: Role of CD4+ T-cell count and NRTI exposure from a large cohort of HIV/HCV-coinfected patients with detectable HCV-RNA: A MASTER cohort study. Medicine (Baltimore) 95: e4091, 2016.
21. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS and Lok AS: A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 38: 518-526, 2003.
22. Federation WaID, World Health Organization (WHO): Definition and diagnosis of diabetes mellitus and intermediate hyperglycarmia. WHO, Geneva, 2006.
23. American Diabetes Association: Classification and diagnosis of diabetes: Standards of medical care in diabetesd-2021. Diabetes Care 44 (Suppl 1): S15-S33, 2021.
24. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of The National cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285: 2486-2497, 2001.
25. Lelis DF, Calzavara JVS, Santos RD, Sposito AC, Griep RH, Barreto SM, Molina MDCB, Schmidt MI, Duncan BB, Bensenor I, *et al*: Reference values for the triglyceride to high-density lipoprotein ratio and its association with cardiometabolic diseases in a mixed adult population: The ELSA-Brasil study. J Clin Lipidol 15: 699-711, 2021.
26. Lertsakulbunlue S, Mungthin M, Rangsin R, Kantiwong A and Sakboonyarat B: Trends in baseline triglyceride-glucose index and association with predicted 10-year cardiovascular disease risk among type 2 diabetes patients in Thailand. Sci Rep 13: 12960, 2023.
27. Zeremski M, Dimova RB, Pillardy J, de Jong YP, Jacobson IM and Talal AH: Fibrosis progression in patients with chronic hepatitis C virus infection. J Infect Dis 214: 1164-1170, 2016.
28. Medrano LM, Garcia-Broncano P, Berenguer J, González-García J, Jiménez-Sousa MÁ, Guardiola JM, Crespo M, Quereda C, Sanz J, Canorea I, *et al*: Elevated liver stiffness is linked to increased biomarkers of inflammation and immune activation in HIV/hepatitis C virus-coinfected patients. AIDS 32: 1095-1105, 2018.
29. Portocarrero Nunez JA, Gonzalez-Garcia J, Berenguer J, Gallego MJV, Loyarte JAI, Metola L, Bernal E, Navarro G, Del Amo J and Jarrín I; and the Cohort of the Spanish HIV Research Network (CoRIS): Impact of co-infection by hepatitis C virus on immunological and virological response to antiretroviral therapy in HIV-positive patients. Medicine (Baltimore) 97: e12238, 2018.
30. Corey KE, Kane E, Munroe C, Barlow LL, Zheng H and Chung RT: Hepatitis C virus infection and its clearance alter circulating lipids: Implications for long-term follow-up. Hepatology 50: 1030-1037, 2009.
31. Miyazaki T, Honda A, Ikegami T, Saitoh Y, Hirayama T, Hara T, Doy M and Matsuzaki Y: Hepatitis C virus infection causes hypolipidemia regardless of hepatic damage or nutritional state: An epidemiological survey of a large Japanese cohort. Hepatol Res 41: 530-541, 2011.
32. Boemeke L, Bassani L, Marroni CA and Gottschall CB: Lipid profile in cirrhotic patients and its relation to clinical outcome. Arq Bras Cir Dig 28: 132-135, 2015 (In English, Portuguese).
33. Del Campo JA and Romero-Gomez M: Modulation of host lipid metabolism by hepatitis C virus: Role of new therapies. World J Gastroenterol 21: 10776-10782, 2015.
34. Liver TAftSot: Thailand Practice Guideline for Management of Chronic Hepatitis B and C 2015. https://thasl.org/en/thasl-guideline-2/.