Original Article

Comparison of Clinical, Biochemical, Virological and Histopathological Characteristics Between Chronic Hepatitis C Infected Patients with Respect to Genotype 1 and 3

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ABSTRACT

Background: Hepatitis C virus (HCV) causes acute and often chronic hepatitis. On the basis of variations in nucleotide sequence, at least six genotypes and several subtypes have been identified. As genotype is considered an important determinant of disease progression and response to anti-viral therapy, we don't know definitely about the difference of each genotype characteristics. The aim of study is to evaluate whether clinical, biochemical, serological and distinct histopathological manifestations of HCV infection are related to particular genotypes of HCV, especially 1 and 3.

Patients and Methods: This study was the case control-retrospective study among 160 pre-treatment chronic hepatitis C patients who underwent liver biopsy at Siriraj Hospital during 1997-2003. Clinical, biochemical liver parameters and histopathological features was analyzed with according to genotype 1 and 3 for the correlation.

Results: The most common genotype in Thai CHC patients was 3 (57% of patients), followed by 1 (37.2%), and 6 (5.8%) which similar to Indian but different from American and European reports. There was no correlation of clinical, biochemical parameters especially liver function tests and quantitative HCV RNA viral load between genotype 1 and 3. However, the most prominent finding of this study is that patients infected with HCV genotype 3 have statistically significant more steatosis than patients infected with genotype 1 ($p < 0.001$, Odds Ratio = 10.84, 95% CI = 2.08-75.36), although they do not differ from patients infected with type 1 regarding inflammatory activity ($p = 0.052$), the degree of fibrosis, the presence of intrahepatic portal lymphoid aggregrates or bile duct damage. Furthurmore, we found that there was no correlation of presence and grade of steatosis with respect to liver necro-inflammatory grading and fibrotic staging including other parameters.

Conclusion: Chronic Hepatitis C genotype 1 and 3 were the common genotype in Thailand. Both were not different in the clinical, biochemical and histopathological features. Only lobular steatosis was the outstanding liver histopathology in genotype 3.

Key words : comparison, chronic hepatitis C, Genotype

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BACKGROUND

The hepatitis C virus (HCV) is one the leading causes of liver disease worldwide.[1] The prevalence of hepatitis C in the general population is 2-3% worldwide[1], the prevalence of HCV in Thailand is about 0.8-2%[2,3] Hepatitis C virus (HCV) causes acute and often chronic hepatitis. On the basis of variations in nucleotide sequence, at least six genotypes and several subtypes have been identified. In the epidemiologic study, genotype 1-3 was found worldwide, genotype 4-5 common in Africa and genotype 6 common in Asia.[4] In more detailed, genotype 1 common in America, Europe and Japan (40-60% compared with 2-20% of genotype 3), but genotype 3 common in India and Thailand (50% compared with 20-30% of genotype 1).[5-11] From the past to the present, the studies about HCV genotypes have been performed mostly in field of outcome of therapy, especially genotype 1 compared with genotype 3. In summary, genotype 3 has the sustained virological response to standard treatment (Peg-interferon+ribavirin) better than genotype 1 (70-80% & 40-50% respectively),[12-14] including duration of treatment shorter than, affecting that genotype to be the most important data before starting treatment as the present consensus.

There were few studies and inconclusive datas about the correlation of clinical, biochemical parameters and histopathological necro-inflammatory grading and fibrotic staging liver injury between genotypes. No definite correlation was found among the most studies.[15-27] In the other histopathological manifestations, the typical "ground glass" inclusions within hepatocytes, which are characteristic for cytoplasmic hepatitis B surface antigen expression, are not apparent in liver sections from chronically HCV-infected patients. In contrast, typical hepatic lesions in chronic HCV infection might include bile duct damage, steatosis, or intrahepatic portal lymphoid clusters or follicles, yielding quite heterogeneous phenotypes of liver injury. Some studies had found more steatosis in genotype 3a and affecting to severity of liver injury,[28-30] but other histopathological features, especially bile duct lesions or portal lymphoid aggregrates, had few and inconclusive datas.[31] Interestingly, there was no datas in Thailand.

The aim of study is to evaluate whether the clinical, biochemical, virological parameters and histopathological manifestations of HCV viral infection are related to particular genotypes (1 and 3) including other variables that had affected to steatosis and treatment responsiveness of chronic hepatitic C patients in Thailand.

PATIENTS AND METHODS

Patients

All patients with chronic hepatitis C who underwent liver biopsy at Siriraj Hospital during 1997-2003 were included in this study and studied retrospectively. The inclusion criteria were patients older than 18 years old who had a positive HCV antibody score by third generation EIA and was confirmed positive HCV-RNA by polymerase chain reaction (PCR). Chronicity was proven by histopathology according to established criteria as described below and by elevated serum alanine transferase(ALT) activities observed for a period longer than 6 months. The exclusion criteria were co-infection with hepatitis B or HIV, previous treatment with anti-viral therapy active against hepatitis C, presence of other liver diseases, inadequate liver biopsy (less than 5 portal triads) and co-existing hepatocellular carcinoma. The study was approved by the local ethical committee of Siriraj Hospital.

Data Collection

Data of all patients enrolled in the study were collected retrospectively for the following parameters:

1. Clinical parameters: age, gender, route of infection, duration of infection, sign of chronic liver disease, hepatomegaly and splenomegaly

2. Biochemical parameters: WBC count, platelet count, prothrombin time, alanine aminotransferase (ALT), AST/ALT ratio, bilirubin, albumin, and albumin/globulin ratio, fasting blood sugar, total cholesterol, triglyceride and body mass index(BMI)

3. Virological parameters: quantitative HCV-RNA assay and HCV genotype

4. Histopathological features was evaluated by single pathologist that was blinded to clinical, biochemical and virological parameters:[32-34]

4.1) Histology Activity Index (HAI) (Knodell's scoring system)[35]

- Necro-inflammatory activity grading by using the combination of portal, periportal and lobular inflammatory scores (mild: 0-6 moderate to severe: 7-18)
- Fibrotic staging (mild: 0-1, severe: 3-4)

4.2) Steatosis (Brunt grading systems)[36]
grade 0: none
grade 1: up to 33%
grade 2: >33-66%
grade 3: >66%
(degree, mild: 0-1, severe: 2-3)

4.3) Intrahepatic portal lymphoid aggregates[15] were defined as a densely packed collection of small lymphocytes and plasma cell infiltrates within the portal tract
score: absent or present (number)

4.4) Bile duct damage[15] was defined as presence of lymphocytes, plasma cell infiltrates with inflammatory cell migration into or between the epithelial cells, variation in nuclear staining, epithelial cell vacuolization, mitotic activity, loss of polarity of epithelial cells, or a combination of these criteria
score: absent or present (number)

Statistical Analysis

Baseline patient characteristics were reported as means ± SD or proportions. The clinical, biochemical, virological parameters and histopathological features were analyzed to determine correlation with HCV genotypes using univariate and multivariate analyses. For univariate analysis, chi-square test or fisher exact test was used for categorical variables whereas unpaired t-test or Mann-Whitney U-test were used for quantitative variables. For multivariate analysis, multiple logistic regression analysis was performed to determine the independent factors. Results were expressed as an adjusted odds ratio (OR) and 95% confidence interval (CI). For all analyses, p values of <0.05 were considered to be statistically significant.

Results

Baseline Patients Characteristics

A total of 114 patients with chronic hepatitis C were included in the study. The mean age was 44.6 ± 10.5 years with a range of 22-66 years. There were 67 male (58.8%) and 47 female (41.2%) patients. Fifty-three of the patients (47.3%) had a blood transfusion history and 8 (7.1%) were former intravenous drug users. However, there was no obvious route of infection was identified upto 35.7%. Average duration of infection was 16.8 years (2-50). Physical examination showed sign of chronic liver disease, hepatomegaly and splenomegaly in only 5%,3% and 2% respectively. Of the biochemical parameters, mean ALT was 150 ± 91 IU/L, mean AST was 96 ± 61 IU/L, mean albumin was 4.2 ± 0.5 gm/dl and albumin/globulin ratio was 1.1 ± 0.3. For virological parameters, the mean HCV RNA level using quantitative PCR was 11.6 ± 20.1 × 10^6 copies/ml. Approximately, more than half of the patients were infected with HCV genotype 3 (60%) and

Table 1 Baseline characteristics of 114 patients

Characteristics	Mean ± SD or n (%)	Characteristics	Mean ± SD or n (%)
Age (yr)	45 (22-66)	WBC (× 10^3)	6.5 ± 1.8
Sex (Male)	67 (58.8%)	Platelet (× 10^3)	194.8 ± 75.9
Route of infection		ALT (IU/L)	150 ± 91
Blood Tx	53 (47.3%)	AST (IU/L)	96 ± 61
IVDU	8 (7.1%)	AST/ALT	0.7 ± 0.2
unknown	40 (35.7%)	TB (mg/dl)	0.8 ± 0.4
other	11 (9.8%)	Albumin (gm/dl)	4.2 ± 0.5
Duration of infection	16.8 (2-50)	Globulin (gm/dl)	4.0 ± 0.7
Sign of CLD	6 (5.4%)	Alb/Glb	1.1 ± 0.3
Hepatomegaly	3 (2.7%)	FBS (mg/dl)	103.1 ± 27.9
Splenomegaly	2 (1.8%)	TC (mg/dl)	182.7 ± 49.2
BMI (kg/m^2)	25.0 ± 3.9	TG (mg/dl)	103.2 ± 53.3
HCV viral load (× 10^6 copies/ml)	11.6 ± 20.1	Rx response	
Genotype 3	69 (60.5%)	SVR	61 (69.3%)
Rx regimens		Relapser	13 (14.8%)
IFN + ribavirin	57 (64.8%)	Non-responder	14 (15.9%)
Peg-IFN + ribavirin	31 (35.2%)		

40% with genotype 1. There were 88 patients that had been treated with both standard (50%) and pegylated (27%) interferon combined with ribavirin. Sixty-one patients out of 88 had sustained a virological response(53.5%), 13 with relapse (11.4%) and 14 with non-response (12.3%). Patients characteristics were summarized in Table 1.

Baseline Liver Histopathological Characteristics

Overall CHC patients had mean HAI score about 7. When necro-inflammation and fibrosis were considered separately, both necro-inflammatory and fibrotic degree were mostly mild (55.3%, 62.3% respectively). Only 9% were cirrhotic. In addition, liver cell inflammation and/or necrosis of lobular and periportal area had mild severity (66.7%, 64.0% respectively) including diffuse form of involvement was also found. But portal area had partial involvement and moderate to severe inflammatory degree (70.2%, 68.4% respectively). Finally, special characteristics that we interested were steatosis, lymphoid aggregration and bile duct involvement. The steatosis was macrovesicular (100%) type and found in diffuse (70.2%) form. Mostly,grading of it was mild (68.4%). Additionally, we also found lymphoid aggregration (70.2%) more common than bile duct injury (14.9%) at simultaneously histologic assessment. Liver histology results were summarized in Table 2

Analysis of Demographic, Biochemical and Virological Parameters in CHC Patients in Relation to Viral Genotype 1and 3

Univariate analysis showed both blood sugar ($p = 0.018$) and BMI ($p = 0.049$) were significantly much higher in genotype 3 whereas only total choles-

Table 2 Baseline histopathological characteristics

Characteristics	Mean ± SD or n (%)	Characteristics	Mean ± SD or n (%)
Portal No.	14 (5-39)		
Lobular degree		Portal degree	
0	8 (7%)	0	1 (0.9%)
1	76 (66.7%)	1	27 (23.7%)
3	28 (24.6%)	3	78 (68.4%)
4	2 (1.8%)	4	8 (7.0%)
Lobular zone		Portal involve.	
0	8 (7%)	Partial	80 (70.2%)
1	1 (0.9%)	Total	27 (23.7%)
2	12 (10.5%)	Normal	1 (0.9%)
4	93 (81.6%)	Equal	6 (5.3%)
Piecemeal deg.		Fibrosis	
0	14 (12.3%)	0	15 (13.2%)
1	73 (64.0%)	1	56 (49.1%)
3	6 (5.3%)	3	34 (29.8%)
5	18 (15.8%)	4	9 (7.9%)
6	3 (2.6%)	Fibrotic degree	
HAI score	7.6 ± 4.1	Mild (0-1)	71 (62.3%)
Mild (<7)	63 (55.3%)	Mod-sev (3-4)	43 (37.7%)
Mod-sev (>7)	51 (44.7%)		
Steatosis deg	Macro (100%)	Lymphoid aggregration	1.8 ± 1.9 (0-10)
0	13 (11.4%)	Present	80 (70.2%)
1	78 (68.4%)	Absent	34 (29.8%)
2	20 (17.5%)		
3	3 (2.6%)		
Steatosis zone		Bile duct involvement	0.3 ± 1.0 (0-7)
0	13 (11.4%)	Present	17(14.9%)
2	19 (16.7%)	Absent	97(85.1%)
3	2 (1.8%)		
total	80 (70.2%)		

terol (p = 0.02) was significantly much higher in genotype 1. When comparing in the part of clinical significance (DM, dyslipidemia, overweight), hypercholesterolemia was much higher in genotype 1. In contrast, there was no statistically significant difference in age, sex, duration of infection, route of infection, sign of chronic liver disease, liver function test (especially AST and ALT), HCV viral load including treatment regimens and responsiveness between genotype 1 and 3. On multivariate analysis, only BMI was much higher in genotype 3. The results of univariate and multivariate analysis were presented in Table 3 and 4 respectively.

Univariate analysis wth regard to HCV genotype revealed that steatosis, rarely occurring in patients infected with HCV genotype 1, was found to be more frequently associated with genotype 3 (p <0.001). Pattern of fat globule deposit of genotype 3 was mostly seen in diffuse form (p = 0.02). Additionally, genotype 3 HCV infection had prominent lobular necrosis in zone 2 (p = 0.01) and moderate to severe piecemeal necrosis (p =0.048) more frequently than genotype 1. In contrast, there was no statistically significant difference found in lobular necrosis degree, steatosis degree, portal inflammation degree and involvement, severity of liver injury (grading and staging) including special characteristics (lymphoid aggregration and bile duct involvement) between genotypes. On multivariate analysis, presence of steatosis, including diffuse involvement, was the outstanding histopathological characteristic of genotype 3 HCV infection [p = 0.003, OR 23.44 (2.85-192.56)]. The results of univariate and multivariate analysis were presented in Table 5 and 6.

Analysis of Variables Associated with Steatosis in CHC Patients

Genotype 3 CHC patients had much higher BMI than genotype 1. In addition, we also found frequently more steatosis than in genotype 3. We uncertainly had known that metabolic (blood sugar, lipid or overweight) and/or viral factors (cytopathic effect) that might affected to fat deposit in liver of HCV infection. Therefore, univariate analysis was performed to answer somethings that we suspected.

Only three variables that correlated with the presence of steatosis included genotype 3 (p <0.001), blood sugar (p = 0.01) and HCV viral load (p = 0.01). In contrast, there was no correlation had been found with age, sex, total cholesterol, triglyceride or other param-

Table 3 Univariate analysis of demographic, biochemical and virological parameters between genotype 1 & 3

Parameters	Genotype 1 (45)	Genotype 3 (69)	p
Age (yr)	46.3 + 9.9	43.6 + 10.8	0.19
Sex (male)	31 (68.9%)	36 (52.2%)	0.07
Blood Tx	25	26	0.78
IVDU	2	6	0.29
Unknown	12	28	0.02
Duration of infection	17.8 + 10.4	16.0 + 7.2	0.4
Hepatomegaly	1 (2.3%)	2 (2.9%)	1.00
Splenomegaly	0	2 (3.0%)	0.51
Sign of CLD	1 (2.3%)	5 (7.5%)	0.40
Platelet ($\times 10^3$)	194.2 + 87.1	195.2 + 68.5	0.79
AST (IU/L)	85.2 + 55.0	103.1 + 64.1	0.12
ALT (IU/L)	150.0 + 87.5	154.3 + 94.0	0.63
TB (mg/dl)	0.8 + 0.4	0.8 + 0.3	0.50
Alb (gm/dl)	4.2 + 0.7	4.3 + 0.5	0.66
Glb (gm/dl)	3.9 + 0.6	4.1 + 0.7	0.37
Alb/Glb	1.1 + 0.2	1.1 + 0.3	0.75
FBS (mg/dl)	93.5 + 12.5	107.8 + 32.1	0.01
FBS >126	1 (5.3%)	7 (17.9%)	0.25
TC (mg/dl)	208.2 + 60.0	167.9 + 34.6	0.00
TC >200	12 (48%)	8 (18.6%)	0.02
TG (mg/dl)	119.0 + 67.4	94.8 + 42.4	0.08
TG >200	3 (13.0%)	1 (2.3%)	0.08
HCV load ($\times 10^6$)	12.3 + 25.4	11.1 + 15.6	0.75
BMI	23.9 + 2.8	25.6 + 4.3	0.049
BMI >25	7 (29.2%)	22 (48.9%)	0.11
SVR			
Yes	26 (76.5%)	48 (88.9%)	0.12
No	8 (23.5%)	6 (11.1%)	
Rx response			
CR	23 (67.7%)	38 (70.4%)	
Relapser	3 (8.8%)	10 (18.5%)	0.21
Non-response	8 (23.5%)	6 (11.1%)	
Rx regimens			
IFN + ribavirin	19 (55.9%)	38 (70.4%)	0.25
Peg + ribavirin	15 (44.1%)	16 (29.6%)	

Table 4 Multivariate analysis. Predictive value for demographic and biochemical parameters between genotype 1 & 3

Parameters	Adjusted Odd Ratio (95%)	p-value
BMI	1.25 (1.00-1.55)	0.048
FBS	1.07 (0.99-1.14)	0.07
TC	0.98 (0.96-1.00)	0.07

Table 5 Univariate analysis of general and special liver histopathological manifestations of genotype 1 & 3

Parameters	Genotype 1 (45)	Genotype 3 (69)	p
Lobular ncrosis			
yes	43 (95.6%)	63 (91.3%)	0.39
Degree			
mild	31 (68.9%)	45 (65.2%)	0.90
mod-severe	12 (26.7%)	18 (26.1%)	0.94
Zone			
Local	1 (2.2%)	12 (17.4%)	0.01
Diffuse	42 (93.3%)	51 (73.4%)	
Portal inf			
yes	45 (100%)	68 (98.6%)	1.0
Degree			
mild	13 (28.9%)	14 (20.3%)	0.31
mod-severe	32 (71.1%)	54 (78.3%)	
Involvement			
Partial	31 (68.9%)	49 (77.8%)	0.39
Total	13 (28.9%)	14 (22.2%)	
Piecemeal necrosis			
yes	42 (93.3%)	58 (84.1%)	0.14
Degree			
mild	35 (83.3%)	38 (65.5%)	0.04
mod-severe	7 (16.7%)	20 (34.5%)	
HAI			
mild	28 (62.2%)	37 (53.6%)	0.37
mod-severe	7 (16.7%)	20 (34.5%)	
Fibrosis			
yes	40 (88.9%)	59 (85.5%)	0.60
Degree			
mild	27 (67.5%)	29 (49.2%)	0.07
mod-severe	13 (32.5%)	30 (50.9%)	
Steatosis			
yes	34 (75.6%)	67 (97.1%)	0.00
Degree			
mild	29 (85.3%)	49 (73.1%)	0.17
mod-severe	5 (14.7%)	18 (26.9%)	
Zone			
Local	11 (32.4%)	10 (14.9%)	
Diffuse	23 (67.7%)	57 (85.1%)	0.02
Lymphoid aggregation			
Yes	31 (68.9%)	49 (71.0%)	0.80
No.	2.9 + 2.3	2.3 ± 1.5	0.14
Bile duct injury			
Yes	9 (20%)	8 (11.6%)	0.22
No.	2.6 + 2.1	1.9 ± 1.2	0.42

Table 6 Multivariate analysis: Predictive value of histopathological finding for genotype 1 & 3

Histopathological finding	Adjusted Odd Ratio (95%)	p-value
Lobular necrosis zone		0.998
Lobular steatosis zone	23.44 (2.9-192.6)	0.003

Table 7 Comparison of clinical, biochemical and virological parameters according to the presence of steatosis in the pre-treatment liver Bx (univariate analysis)

Characteristics	Pt. with steatosis (101)	Pt. without steatosis (13)	p-value
Age (yr)	44.8 ± 9.8	42.9 ± 15.3	0.66
Sex (male)	59 (58.4%)	8 (61.5%)	0.83
BMI (kg/m^2) (62)	25.2 ± 3.8	23.0 ± 4.3	0.15
BMI >25	21 (43.6%)	35 (56.5%)	0.44
FBS (mg/dl) (58)	104.4 ± 28.9	89.2 ± 8.1	0.01
FBS >126	8 (17.8%)	0	1.00
TC (mg/dl) (68)	181.0 ± 45.2	195.5 ± 75.8	0.61
TC >200	17 (39.5%)	3 (60%)	0.68
TG (mg/dl) (66)	101.2 ± 48.4	118.1 ± 83.5	0.40
TG >200	2 (3.5%)	2 (33.3%)	0.07
AST (IU/L)	96.8 ± 62.3	90.5 ± 51.9	0.73
ALT (IU/L)	150.5 ± 90.2	154.5 ± 102.0	0.88
HCV viral load (× 10^5 copies/ml)	12.5 ± 20.9	3.6 ± 6.8	0.01
Genotype 3 (69)	67 (67.3%)	2 (15.4%)	<0.001

eters. On multivariate analysis, steatosis was only correlated with genotype 3 (p = 0.015). The results of univariate and multivariate analysis were presented in Table 7 and 8.

Analysis the Correlation Between Degree of Steatosis and Severity of Liver Injury Including Variables that Affected to Severity in Genotype 3 HCV Infected Patients

Presence and degree of steatosis in genotype 3 HCV infectious patients did not have the correlation with severity of liver cell injury both necroinflammatory grading and fibrotic staging (p = 0.12, p = 0.70 respectively). But severity of liver cell inflammation and fibrotic stage had the correlation each other (p = 0.00) both genotype 1 and 3. Other variables, that had affected to liver injury in genotype 3, were age and AST level (p = 0.00, p = 0.001 respectively). CHC

Table 8 Multivariate analysis:Predictive value of clinical, biochemical and virological parameters according to the presence of steatosis in the pre-treatment liver biopsy

Characteristics	Adjusted Odd Ratio (95%)	p-value
Genotype 3	14.1 (1.7-118.2)	0.02
HCV viral load ($\times 10^6$ copies/ml)		0.58

Table 9 Univariate analysis for variables associated with grading of liver injury

Parameters	Genotype 3 mild	Genotype 3 mod-severe	p
Age (yr)	38.7 ± 9.9	49.2 ± 8.9	0.00
AST (IU/L)	79.4 ± 42.7	130.5 ± 73.8	0.00
ALT (IU/L)	139.3 ± 171.3	86.6 ± 135.5	0.16
HCV load	13.2 ± 17.1	8.7 ± 13.5	0.29
Steatosis (yes)	36 (97.3%)	31 (96.9%)	1.00
Steatosis >1	13 (36.1%)	5 (16.1%)	0.12
Fibrosis >2	1 (3.7%)	90.6%)	0.00
Response CR:relapse:nonresponse	21:1:4	17:9:2	0.02

Parameters	Genotype 1 mild	Genotype 1 mod-severe	p
Age (yr)	44.7 ± 10.5	48.2 ± 8.8	0.24
AST (IU/L)	75.2 ± 51.5	98.9 ± 57.9	0.16
ALT (IU/L)	135.4 ± 87.6	160.5 ± 87.5	0.35
HCV load	13.7 ± 24.5	10.7 ± 27.0	0.73
Steatosis (yes)	17 (65.4%)	17 (89.5%)	0.09
Steatosis >1	2 (11.8%)	3 (17.6%)	1.00
Fibrosis >2	1 (5%)	12 (70.6%)	0.00
Response CR:relapse:nonresponse	12:1:4	11:2:4	1.00

patients who had old age and high AST, might respond to treatment less than younger patients with low AST. The results were presented in Table 9 and 10.

DISCUSSION

The comparison of histopathological features in relation to HCV genotype is not readily possible unless differences regarding demographic data, eg:patient's age and history of drug abuse, biochemical and virological data are taken into consideration. In this study, the most prominent finding is that patients infected with HCV genotype 3 frequently had

Table 10 Univariate analysis for variables associated with fibrotic stage of liver injury

Parameters	Genotype 3 mild	Genotype 3 mod-severe	p
Age (yr)	39.2 ± 10.0	49.6 ± 8.7	0.00
AST (IU/L)	84.1 ± 44.8	135.2 ± 73.3	0.002
ALT (IU/L)	138.1 ± 82.8	181.9 ± 106.9	0.08
HCV load ($\times 10^6$ copies/ml)	10.5 ± 15.8	11.7 ± 16.9	0.80
Steatosis (yes)	28 (96.6%)	29 (96.7%)	1.00
Steatosis >1	8 (28.6%)	6 (20.7%)	0.70
HAI >7	3 (10.3%)	29 (96.7%)	0.00
Rx response CR:relapse:non-response	16:1:4	15:9:2	0.03

Parameters	Genotype 1 mild	Genotype 1 mod-severe	p
Age (yr)	44.9 ± 10.5	50.8 ± 8.6	0.09
AST (IU/L)	80.6 ± 50.6	103.9 ± 69.7	0.24
ALT (IU/L)	149.7 ± 91.6	136.3 ± 69.7	0.65
HCV load ($\times 10^6$ copies/ml)	13.9 ± 27.9	6.4 ± 14.7	0.41
Steatosis(yes)	18 (69.2%)	11 (84.6%)	0.45
Steatosis >1	1 (5.6%)	4 (57.1%)	0.054
HAI >7	7 (26.9%)	12 (92.3%)	0.000
Rx response CR:relapse:non-response	14:2:5	7:1:3	1.00

significantly more steatosis and body mass index (BMI) than patients infected with genotype 1. The result of presence steatosis was similar to the mostly other studies. There was no statistically significant difference in our study about clinical parameters (old age, blood transfusion, longer duration of infection, severe HAI and fibrotic score) and genotype 1 and 3. Additionally, HCV genotype 3-infected patients had lower serum cholesterol levels compared to patients infected genotype 1. The difference in serum cholesterol levels between genotype had a few data. But in our study, it was similar to a study by Sharma *et al*.[37]

Hepatic steatosis is a frequent finding in patients with chronic hepatitis C. In this study steatosis was present in 88.6% of patients. Lipid accumulation in chronic hepatitis C patients may be a direct consequence of HCV infection or secondary to host factors or both.[38] Therefore, it is suggested that hepatitis C may itself predispose towards the development of hepatic steatosis and improved in patients who achieve sustained virological response following interferon therapy.[39,40] Furthermore, hepatic steatosis associated

with genotype 3 correlated directly with serum HCV RNA viral load in univariate analysis. For this reason, it may attribute to support direct viral effect in as the hypothesis about pathogenesis of steatosis.[41-47] But other host factors espectially metabolic syndromes (overweight, DM and hyperlipidemia) that might or might not affected to steatotic development were not definitely concluded because of small populations in this situations. Additionally, severity of steatosis had no statistically significant difference between genotypes in our study. When comparing to the other studies in Europe,[48,49] prevalence and grade of steatosis were strongly associated with HCV genotype 3.

From the previous studies we found that presence and grade of steatosis had the correlation with severity of liver injury both necroinflammation and fibrosis including progression of liver fibrosis.[49-53] But we did not found such correlation in our study and could not conclude about its progression due to the cross sectional study.[54] Both grade and stage of liver disease also had the correlation each other in genotype 1 and 3. In addition, we found that only HCV-genotype 3 infected patients, who had old age and high AST, might have trend to be more severity of liver injury. Exceptionally, old age and high serum AST level may be predictors for more severe necro-inflammation and fibrosis in HCV-genotype 3 infected patients.

CONCLUSION

In this study, we found that presence of steatosis was common in HCV-genotype 3 infection. Pathogenesis of fat accumulation may be cytopathic effect of virus itself. Additionally, presence and grade of steatosis had no correlation with severity of liver injury. Both old age and high serum AST may predicted more severe necro-inflammation and more severe fibrosis in only genotype which may be alleviate the need for liver biopsy.

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