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# A Lower Serum Gamma-Glutamyltransferase Level Does Not Predict a Sustained Virological Response in Patients with Chronic Hepatitis C Genotype 1

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**Background/Aims:** Low gamma-glutamyltransferase (GGT) level was shown to be an independent predictor of a sustained virological response (SVR) in chronic hepatitis C. We aimed to determine factors associated with high GGT level, and to evaluate whether low GGT level is an independent predictor of a SVR in chronic hepatitis C genotype 1. **Methods:** We retrospectively reviewed our data of patients with chronic hepatitis C genotype 1 treated with pegylated interferon-α and ribavirin. Baseline features were compared between patients with normal and high GGT levels. Factors associated with high GGT level and those associated with a SVR were determined by univariate and multivariate analysis. **Results:** This study included 57 patients. Mean age was 52.28±9.35 years. GGT levels was elevated in 27 patients (47.4%). GGT levels were normal in 63.3% of the patients who achieved a SVR and in 40.7% of those who did not achieve a SVR (p>0.05). By multivariate logistic regression analysis, the presence of cirrhosis (odds ratio [OR], 9.41; 95% confidence interval [CI], 1.08 to 102.61) and female gender (OR, 6.77; 95% CI, 1.23 to 37.20) were significantly associated with high GGT level, and only rapid virological response was associated with a SVR (OR, 8.369; 95% CI, 1.82 to 38.48). **Conclusions:** Low GGT level does not predict a SVR; however, it may be a predictor of high fibrosis scores. **(Gut Liver 2013;7:74-81)**

**Key Words:** Chronic hepatitis C; Gamma-glutamyltransferase

## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the most common cause of cirrhosis and hepatocellular carcinoma (HCC), and cirrhosis from chronic HCV infection is also the major indication for liver transplantation.[1,2]

Current guidelines recommended 48 weeks of treatment with pegylated interferon-α (PegIFN-α) and ribavirin combination for chronic HCV genotype 1 infection.[1-3] A sustained virological response (SVR) can be attained in 40% to 60% of patients with this regimen.[4-8]

The likelihood of achieving a SVR can be predicted by both pretreatment and on-treatment variables. Genotype and baseline serum HCV RNA level are the most important pretreatment predictors of a SVR. A SVR is more likely in patients with HCV genotype 2 and 3 and in those with low serum HCV RNA levels.[5-7,9-11] Other pretreatment predictors of a SVR are the absence of bridging fibrosis or cirrhosis on liver biopsy, the absence of hepatosteatosis, high serum alanine aminotransferase (ALT) levels, lower body weight, the absence of insulin resistance, and younger age.[6-13]

The most important on-treatment predictor of a SVR is the rapidity of decline in serum HCV RNA levels. A rapid virological response (RVR) is the most important predictor of a SVR independent of genotype, whereas failure to achieve an early virological response (EVR) is the most important predictor of not achieving a SVR.[5,8,9,13-16] Low pegylated IFN-α and ribavirin dosages because of nonadherence or intolerance adversely affects SVR.[8,16,17]

Serum gamma-glutamyltransferase (GGT) levels have shown to be elevated in 32% to 63% of patients with chronic HCV infection.[11,18-20] In some studies, low baseline GGT level was shown to be an independent predictor of a SVR.[9-11,13,15,17] However, these studies did not fully evaluate other confounding factors, such as the presence of hepatosteatosis,[19,21,22] bile duct injury,[19,23]

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the degree of liver fibrosis,[11,20] alcohol abuse,[18,24] and gender,[17] which might affect both GGT levels and SVR rates.

In this study, we aimed to determine factors which affect serum GGT levels, and to evaluate whether low baseline serum GGT level is an independent predictor of a SVR in patients infected with HCV genotype 1.

## MATERIALS AND METHODS

We retrospectively reviewed our computerized data of chronic hepatitis C patients who were treated with PegIFN α-2a 180 μg/wk and weight based ribavirin (<75 kg, 1,000 mg/day; ≥75 kg, 1,200 mg/day) combination or PegIFN α-2b 1.5 μg/kg/wk and weight based ribavirin (<65 kg, 800 mg/day; 65 to 85 kg, 1,000 mg/day; 85 to 105 kg, 1,200 mg/day; >105 kg, 1,400 mg/day) combination from 2005 to 2009 in Gastroenterology Clinic. Of the 137 patients, 57 with the following criteria were included in this study: 1) anti-HCV and HCV RNA positivity within 6 months prior to therapy, 2) available quantitative serum HCV RNA levels at the beginning, at weeks 12, 24, and 48 of therapy, and 24 weeks after completion of therapy, 3) presence of moderate-to-severe necroinflamatory activity or significant fibrosis (Metavir F2-4) on liver biopsy, 4) absence of HCC, 5) abstinence from alcohol abuse for more than 6 months, and 6) adherence to therapy (defined as at least 80% of the scheduled therapy dosage and duration).

Eighty patients were excluded from the study. Of these patients, 18 patients did not have available data of genotype, quantitative serum HCV RNA levels prior to or during therapy, 11 patients had non-genotype 1 infection, seven patients did not have liver biopsy specimens, and 19 had chronic kidney failure. Fourteen patients were excluded because therapy had been discontinued early due to adverse effects or complications. Also, 11 nonadherent patients were excluded.

Baseline serum aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), and GGT values were recorded. These biochemical values were considered as an index according to the upper limit of normal (ULN). HCV RNA levels were measured using reverse transcription-polymerase chain reaction. Baseline serum HCV RNA level <800,000 IU/mL was classified as low level viremia and that ≥800,000 IU/mL as high level viremia. Genotype was determined using a reverse hybridization assay.

RVR was defined as undetectable serum HCV RNA at week 4 of therapy. Complete EVR (cEVR) was defined as undetectable serum HCV RNA at week 12 of therapy and partial EVR (pEVR) as detectable serum HCV RNA but at least 2 log decline from baseline at week 12 of therapy. End of treatment response was defined as undetectable serum HCV RNA at the end of therapy. SVR was defined as undetectable serum HCV RNA 24 weeks following completion of therapy. Because serum HCV RNA levels were not measured in all patients at week 4 of therapy, all patients who were negative for serum HCV RNA at week 12 of therapy were defined as cEVR regardless of serum HCV RNA levels at week 4 of therapy.

Body mass index (BMI) was calculated according to the following formula: BMI ($kg/m^2$)=weight (kg)/height $(m)^2$.

All liver biopsy specimens were analyzed by a single experienced pathologist. The degree of necroinflamatory activity (grade) and fibrosis (stage) were scored according to the Metavir system. No fibrosis was defined as F0, mild fibrosis as F1, moderate fibrosis as F2, severe fibrosis as F3, cirrhosis as F4, and no inflammation as A0, mild inflammation as A1, moderate inflammation as A2, severe inflammation as A3. Significant fibrosis was defined as F2-4. Liver biopsy specimens were also analyzed for the presence of hepatosteatosis and bile duct injury.

### Statistical analysis

Baseline demographic, biochemical, and histopathologic features were compared between patients with normal serum GGT index (≤1×ULN) and those with high GGT index (>1×ULN). Factors associated with high serum GGT levels were determined by univariate and multivariate analysis. Baseline demographic, biochemical, and histological features were compared between patients who achieved an SVR and those who did not achieve an SVR, and predictors of SVR were defined by univariate and multivariate analysis.

Student's t-test and Mann Whitney U test were performed when comparing the quantitative variables between the groups. Chi-squared test and Fisher's exact chi-squared test were performed when comparing the qualitative variables between the groups. Logistic regression analysis was performed in multivariate analysis. A $p<0.05$ was considered as statistically significant. Statistical analysis were made using NCSS (NCSS Statistical Software, Kaysville, UT, USA) 2007 and PASS (NCSS Statistical Software) 2008 Statistical Software.

This study was carried out according to the Declaration of Helsinki 2004, and the study protocol was approved by the ethics committee of the institution. Written informed consent was obtained from patients.

## RESULTS

### 1. Baseline characteristics

Fifty-seven patients with chronic genotype 1 HCV infection who were treated with PegIFN and ribavirin combination for 48 weeks were included in this study. All patients were white and 47.4% of whom were male (n=27) with a mean age of 52.28±9.35 years. Information on the BMI was available for 49 patients. The mean BMI was 29.4±4.5 $kg/m^2$. None of the patients had a history of alcohol abuse within 6 months prior to therapy.

The mean serum AST (×ULN), ALT (×ULN), ALP (×ULN),

and GGT (×ULN) levels were 1.69±1.08 (range, 0.65 to 6.88), 1.59±0.80 (range, 0.40 to 4.13), 0.62±0.23 (range, 0.27 to 1.41), and 1.32±1.07 (range, 0.21 to 5.80), respectively. Serum GGT levels were >1×ULN in 27 (47.4%) of the patients. The mean serum HCV RNA level was 5,697,425±10,091,987 IU/mL (range, 62,994 to 61,490,000) and 44 (77.2%) had serum HCV RNA levels ≥800,000 IU/mL.

Thirty-two (56.1%) patients had significant fibrosis (F2-4), 11 (19.3%) had cirrhosis (F4) and 21 (36.8%) had moderate-to-severe necroinflammatory activity scores (A2-3) on liver biopsy. The liver biopsy showed hepatosteatosis in 26 (45.6%) patients and bile duct injury in 32 (56.1%) patients.

Baseline characteristics of patients are shown in Table 1.

**Table 1.** Baseline Patient Characteristics

| Characteristic | Value |
|---|---|
| Demographic features | |
| Age | 52.28±9.35 (27–72) |
| Age ≥50 | 38 (66.7) |
| Male gender | 27 (47.4) |
| BMI, kg/m$^2$ | 29.4±4.5 (17.3–37.6) |
| BMI ≥30 | 22 (44.9) |
| Weight, kg | 75.30±12.44 (41–107) |
| Laboratory | |
| AST (×ULN) | 1.69±1.08 (0.65–6.88) |
| AST (×ULN) ≥1.3 | 31 (54.4) |
| ALT (×ULN) | 1.59±0.80 (0.40–4.13) |
| ALT (×ULN) ≥1.3 | 34 (59.6) |
| ALP (×ULN) | 0.62±0.23 (0.27–1.41) |
| ALP (×ULN) ≥1 | 5 (8.8) |
| GGT (×ULN) | 1.32±1.07 (0.21–5.80) |
| GGT (×ULN) >1 | 27 (47.4) |
| HCV RNA, IU/mL | 5,697,425±10,091,987 (62,994–61,490,000) |
| HCV RNA ≥800,000 IU/mL | 44 (77.2) |
| Liver biopsy | |
| Stage | 1.82±1.39 (0–40) |
| Significant fibrosis (F2-4) | 32 (56.1) |
| Cirrhosis (F4) | 11 (19.3) |
| Grade | 1.54±0.82 (0–3) |
| Grade (A2-3) | 21 (36.8) |
| Hepatosteatosis | 26 (45.6) |
| Bile duct injury | 32 (56.1) |

Data are presented as mean±SD (range) or number (%).
BMI, body mass index; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; HCV, hepatitis C virus; RNA, ribonucleic acid.

### 2. Univariate analysis of variables associated with high serum GGT levels

Baseline factors that could be associated with high serum GGT levels were compared between patients with normal and high serum GGT levels (Table 2). Patients with high serum GGT levels tended to be female and obese.

The presence of moderate-to-severe necroinflammatory activity scores, significant fibrosis, cirrhosis, hepatosteatosis, and bile duct injury were more frequently seen in patients with high serum GGT levels than those with normal serum GGT levels. Serum AST, ALT, and ALP levels were also higher in patients with high serum GGT levels. Serum HCV RNA levels were similar in patients with normal and high serum GGT levels.

Serum GGT levels were significantly correlated with serum AST, ALT, and ALP levels (Table 3).

### 3. Multivariate analysis of variables associated with high serum GGT levels

Baseline demographic and histopathological factors that were significantly associated with high serum GGT levels by univariate analysis were then analyzed by multivariate analysis. Gender, BMI (≥30 kg/m$^2$), presence of cirrhosis (F4), moderate-to-severe necroinflammatory activity, hepatosteatosis, and bile duct injury were evaluated by logistic regression analysis. After logistic regression analysis, presence of cirrhosis (odds ratio [OR], 9.41; 95% confidence interval [CI], 1.08 to 102.61) and female gender (OR, 6.77; 95% CI, 1.23 to 37.20) were significantly associated with high serum GGT levels independent of other factors (Table 4).

### 4. Univariate analysis of variables associated with a SVR

Baseline factors that could be associated with a SVR were compared between patients with and without SVR (Table 5). Patients with and without a SVR were similar in age, gender, and BMI. Low or high pretreatment viral load, serum AST, and ALP levels were also similar in patients with and without a SVR. Serum GGT levels were higher in patients without a SVR than those without a SVR, although the difference did not reach statistical significance (p=0.088).

The presence of moderate-to-severe necroinflammatory activity scores, cirrhosis, hepatosteatosis, and bile duct injury were similar in patients with and without a SVR. The presence of significant fibrosis was more likely in patients without a SVR than those with a SVR.

The proportion of patients with either a RVR or cEVR were significantly higher in patients with a SVR than those without a SVR. A SVR was achieved in 77.8% of patients with a RVR and in 63.8% of those with cEVR, whereas non of the patients with pEVR achieved a SVR.

**Table 2.** Comparison of Variables between Patients with Normal and High Serum GGT Levels

| Variable | | Normal GGT (n=30) | High GGT (n=27) | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Age | >50 | 19 (50) | 19 (50) | 1.375 | 0.574 |
| | <50 | 11 (57.9) | 8 (42.1) | (0.453–4.175) | |
| Gender | Female | 10 (33.3) | 20 (66.7) | 5.714 | 0.002* |
| | Male | 20 (74) | 7 (26) | (1.81–18.0) | |
| BMI (n=57) | >30 | 8 (36.4) | 14 (63.6) | 3.500 | 0.035† |
| | <30 | 18 (66.7) | 9 (33.3) | (1.074–11.402) | |
| HCV RNA | ≥800,000 | 23 (52.3) | 21 (47.7) | 1.065 | 0.920 |
| | <800,000 | 7 (53.9) | 6 (46.1) | (0.308–3.683) | |
| Grade | 2–3 | 6 (28.6) | 15 (71.4) | 5.000 | 0.005* |
| | 0–1 | 24 (66.7) | 12 (33.3) | (1.547–16.162) | |
| Significant fibrosis | Present | 11 (34.4) | 21 (65.6) | 6.045 | 0.002* |
| | Absent | 19 (76) | 6 (24) | (1.872–19.256) | |
| Cirrhosis | Present | 2 (18.9) | 9 (81.1) | 7.000 | 0.011† |
| | Absent | 28 (60.9) | 18 (39.1) | (1.354±36.180) | |
| Hepatosteatosis | Present | 9 (34.6) | 17 (65.4) | 3.967 | 0.013† |
| | Absent | 21 (67.7) | 10 (32.3) | (1.314–11.970) | |
| Bile duct injury | Present | 13 (40.1) | 19 (59.9) | 3.106 | 0.040† |
| | Absent | 17 (68) | 8 (32) | (1.037–9.304) | |
| AST (×ULN) | ≥1.3 | 10 (32.3) | 21 (67.7) | 7.000 | 0.001* |
| | <1.3 | 20 (76.9) | 6 (23.1) | (2.145–22.848) | |
| ALT (×ULN) | ≥1.3 | 14 (41.2) | 20 (58.8) | 3.265 | 0.035† |
| | <1.3 | 16 (69.6) | 7 (30.4) | (1.065–10.012) | |
| ALP (×ULN) | >1 | 0 | 5 (100) | 0.423 | 0.014† |
| | <1 | 30 (57.7) | 22 (42.3) | (0.308–0.581) | |

Data are presented as number (%). Chi-square test.
GGT, gamma-glutamyltransferase; OR, odds ratio; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus; RNA, ribonucleic acid; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase.
*p<0.01; †p<0.05.

**Table 3.** Correlation between Serum GGT Levels and Serum AST, ALT, and ALP Levels

| Variable | GGT | |
|---|---|---|
| | r* | p-value |
| AST | 0.647 | 0.001† |
| ALT | 0.431 | 0.001† |
| ALP | 0.600 | 0.001† |

GGT, gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.
*Pearson correlation coefficient; †p<0.01.

**Table 4.** Multivariate Analysis of Factors Associated with a High Serum GGT Level

| Variable | p-value | OR | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Female gender | 0.028 | 6.77 | 1.23 | 37.20 |
| BMI (≥30) | 0.072 | 5.71 | 0.85 | 38.12 |
| Cirrhosis (F4) | 0.046 | 9.41 | 1.08 | 102.61 |
| Hepatosteatosis | 0.177 | 3.16 | 0.59 | 16.84 |
| Bile duct injury | 0.156 | 4.10 | 0.58 | 28.88 |
| Grade (A2-3) | 0.301 | 2.57 | 0.43 | 15.48 |

GGT, gamma-glutamyltransferase; OR, odds ratio; CI, confidence interval; BMI, body mass index.

### 5. Multivariate analysis of variables associated with a SVR

Baseline and treatment factors that were significantly associated with a SVR by univariate analysis were then analyzed by multivariate analysis. Age, serum HCV RNA levels, serum ALT levels, serum GGT levels, presence of significant fibrosis (F2-4) and RVR were evaluated by logistic regression analysis. After logistic regression analysis, only RVR was associated with a SVR (OR, 8.369; 95% CI, 1.82 to 38.48) (Table 6).

**Table 5.** Comparison of Variables between Patients with and without a SVR

| Variable | | SVR (n=30) | Non-SVR (n=37) | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Pretreatment | | | | | |
| Age | <50 | 12 (63.2) | 7 (36.8) | 1.905 | 0.260 |
| | >50 | 18 (47.4) | 20 (52.6) | (0.616–5.890) | |
| Gender | Female | 17 (54.8) | 14 (45.2) | 0.824 | 0.716 |
| | Male | 13 (50) | 13 (50) | (0.290–2.340) | |
| BMI (n=56) | >30 | 13 (59.1) | 9 (40.9) | 1.556 | 0.445 |
| | <30 | 13 (48.1) | 14 (51.9) | (0.499–4.848) | |
| HCV RNA | <800,000 | 9 (69.2) | 4 (30.8) | 2.646 | 0.172 |
| | ≥800,000 | 21 (47.7) | 23 (52.3) | (0.660–9.200) | |
| AST (×ULN) | <1.3 | 15 (60) | 10 (40.0) | 1.700 | 0.325 |
| | ≥1.3 | 15 (46.9) | 17 (53.1) | (0.580–4.900) | |
| ALT (×ULN) | <1.3 | 16 (69.6) | 7 (30.4) | 3.265 | 0.035* |
| | ≥1.3 | 14 (41.2) | 20 (58.8) | (1.065–10.010) | |
| ALP (×ULN) | <1 | 29 (55.8) | 23 (44.2) | 5.043 | 0.126 |
| | ≥1 | 1 (20.0) | 4 (80.0) | (0.530–48.260) | |
| GGT (×ULN) | ≤1 | 19 (63.3) | 11 (40.7) | 2.512 | 0.088 |
| | >1 | 11 (36.7) | 16 (59.3) | (0.863–7.310) | |
| Grade | 2–3 | 13 (61.9) | 8 (38.1) | 1.816 | 0.284 |
| | 0–1 | 17 (47.2) | 19 (52.8) | (0.606–5.441) | |
| Significant fibrosis | Present | 17 (68) | 8 (32) | 3.106 | 0.040* |
| | Absent | 13 (40.6) | 19 (59.4) | (1.037–9.304) | |
| Cirrhosis | Present | 26 (56.5) | 20 (43.5) | 2.275 | 0.229 |
| | Absent | 4 (36.4) | 7 (63.6) | (0.584–8.862) | |
| Hepatosteatosis | Present | 13 (48.1) | 14 (51.9) | 0.710 | 0.520 |
| | Absent | 17 (56.7) | 13 (43.3) | (0.250–2.018) | |
| Bile duct injury | Present | 15 (46.9) | 17 (53.1) | 1.700 | 0.325 |
| | Absent | 15 (60) | 10 (40) | (0.589–4.904) | |
| Treatment | | | | | |
| RVR | Present | 14 (77.8) | 4 (22.2) | 7.350 | 0.002† |
| | Absent | 10 (32.3) | 21 (67.7) | (1.920–28.135) | |
| Complete EVR | Present | 30 (63.8) | 17 (36.2) | – | 0.001† |
| | Absent | 0 | 10 (100) | | |

Data are presented as number (%). Chi-square test and/or Fisher's exact test.
SVR, sustained virological response; OR, odds ratio; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus; RNA, ribonucleic acid; AST, aspartate aminotransferase; ULN, upper limit of normal; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl-transferase; RVR, rapid virological response; EVR, early virological response.
*p<0.05; †p<0.01.

## DISCUSSION

In previous studies, serum GGT levels were shown to be elevated in 32% to 63% of patients with chronic hepatitis C.[11,18-20] In our study, serum GGT levels were elevated in 47% of the patients.

In the present study, we evaluated factors that could be associated with high serum GGT levels in patients with chronic hepatitis C. In univariate analysis, female gender, obesity (BMI ≥30 kg/m$^2$), presence of high necroinflammatory activity and fibrosis scores, hepatosteatosis and bile duct injury, and high serum AST and ALT levels were associated with high serum GGT levels. Of these factors, female gender and presence of cirrhosis were associated with high serum GGT levels in multivariate analysis.

Some of our findings were consistent with previous studies. In the present study, the only histological factor associated with high serum GGT level was the presence of cirrhosis. However, we did not find an association between high serum GGT levels and the presence of either significant fibrosis or high necroinflammatory activity. Forns *et al*.[20] showed that serum GGT level

**Table 6.** Multivariate Analysis of Factors Associated with a SVR

| Variables | p-value | OR | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age (<50) | 0.166 | 2.781 | 0.65 | 11.83 |
| HCV RNA (<800,000) | 0.210 | 2.746 | 0.56 | 13.32 |
| ALT (<1.3) | 0.142 | 2.943 | 0.69 | 12.44 |
| GGT (≤1) | 0.334 | 2.113 | 0.46 | 9.64 |
| Fibrosis (0–1) | 0.910 | 0.914 | 0.19 | 4.33 |
| RVR | 0.006 | 8.369 | 1.82 | 38.48 |

SVR, sustained virological response; OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus; RNA, ribonucleic acid; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; RVR, rapid virological response.

was one of the independent predictors of significant fibrosis and proposed a noninvasive fibrosis test including serum GGT level. Subsequently, Thabut *et al*.[25] found similar results. However, these studies did not evaluate the association between serum GGT levels and the presence of cirrhosis and necroinflammatory activity.[20] In study of Parise *et al*.,[26] serum GGT level ≥1.5×ULN and ≥2×ULN were indepentent predictors of significant fibrosis and cirrhosis, respectively. Silva *et al*.[19] also showed that high serum GGT level was associated with high necroinflammatory acitivity and high fibrosis scores. When we take into account these findings, association between high serum GGT levels and the presence of cirrhosis in our study is not surprising. The correlation between serum GGT and serum AST levels also supports this finding, because these enzymes are known to be elevated as the degree of fibrosis progresses.[27-29]

The presence of bile duct injury has been shown in chronic hepatitis C patients.[11,18,19,23] In study of Hwang *et al*.,[23] bile duct injury was demonstrated in 71% of patients with chronic hepatitis C and it was shown that genotype 1b, high portal inflammation score and high portal lymphoid aggregate/follicle were independent predictors of bile duct injury. However, serum GGT levels were not different between patients with and without bile duct injury.[23] Similarly, Silva *et al*.[19] did not find an association between serum GGT level and bile duct injury. On the other hand, Giannini *et al*.[18] showed that serum GGT levels were more frequently elevated in patients with bile duct injury and that high serum GGT level was the only biochemical predictor of bile duct injury in patients with chronic hepatitis C. Although bile duct injury was present in half of the patients, there was not an association with serum GGT level and bile duct injury.

Hepatosteatosis is also frequent in chronic hepatitis C. Hepatosteatosis was present in 47% of our patients. Silva *et al*.[19] showed that hepatosteatosis was present in 73% of patients with chronic hepatitis C, but there was not an association between serum GGT levels and hepatosteatosis, similar to our study. However, it should be kept in mind that the present study included only those patients with genotype 1 HCV infection, as the prevalance of hepatosteatosis differs between genotypes.[30,31]

The other interesting findings of our study are that female gender was an independent predictor of high serum GGT levels and that there was not an association between age and serum GGT levels, since it is known that serum GGT levels are higher in men and increase with age.[32] Although it did not reach statistical significance, serum GGT levels were higher in patients with higher BMI.

The second aim of the present study was to evaluate whether low serum GGT level was an independent predictor of a SVR. In univariate analysis, low serum ALT level, absence of significant fibrosis (F2-4), RVR, and cEVR were associated with achieving a SVR. However, logistic regression analysis revealed that only RVR was an independent predictor of a SVR. A SVR was 2.1 times more likely in patients with normal serum GGT levels than those with high serum GGT levels, but this was not statistically significant.

Since it has been shown that RVR was one of the most important predictors of a SVR,[8,9,11,13-15] this result of the present study was not interesting.

On the other hand, the finding that normal serum GGT level was not an independent predictor of a SVR was not consistent with previous studies. High rates of response to therapy were shown in patients with chronic hepatitis C with low serum GGT levels by Mazzella *et al*.[33] in 1994 and by Mihm *et al*.[34] in 1996. Subsequently, many studies have revealed that normal or lower serum GGT level was an independent predictor of a SVR in chronic hepatitis C.[9-11,15,17] On the other hand, Grasso *et al*.[12] did not find an association between serum GGT level and SVR similar to our study. However, it should be kept in mind that some previous studies did not take into account the degree of necroinflammatory activity, presence of bile duct injury and hepatosteatosis.[10,11,15] Akuta *et al*.[17] did not consider the degree of necroinflammatory activity and presence of bile duct injury and Berg *et al*.[9] did not consider the presence of bile duct injury and hepatosteatosis, when considering low serum GGT level as an independent predictor of SVR. In contrast to previous studies, we evaluated all these factors when considering whether low serum GGT level was an independent predictor of a SVR. The limitation of the present study might be that we did not take into account some factors such as insulin resistance, uric acid and cholesterol levels which might affect both SVR rates and serum GGT level.

In conclusion, presence of cirrhosis and female gender were independent predictors of high serum GGT level. In contrast to previous studies that found normal or low serum GGT level as an independent predictor of a SVR, we did not find an association between serum GGT level and SVR in the whole cohort. This might be due to our study design in which we evaluated more histological factors that might lead to both high serum GGT levels and lower SVR rates. Even though normal serum GGT level was an independent predictor of a SVR in female

patients in the present study, it should be kept in mind that the number of patients was limited to make a certain consideration.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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