Accepted Manuscript

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PII: S0168-8278(12)00626-5
DOI: http://dx.doi.org/10.1016/j.jhep.2012.07.045
Reference: JHEPAT 4372

To appear in: Journal of Hepatology

Received Date: 4 April 2012
Revised Date: 13 July 2012
Accepted Date: 31 July 2012


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Myocardial injury in patients with chronic hepatitis C infection

Shigeo Maruyama ¹, Masahiko Koda ², Nobuyuki Oyake ³, Hidetoshi Sato ⁴,
Yasuyoshi Fujii ⁵, Yutaka Horie ⁵, Yoshikazu Murawaki ²

1) Maruyama Medical Clinic, Hamada, Japan
2) Second Department of Internal Medicine, Faculty of Medicine, Tottori University,
Yonago, Japan
3) Otsuka Clinic, Izumo, Japan
4) Forth Department of Internal Medicine, Shimane University, Izumo, Japan
5) Second Department of Internal Medicine, Saiseikai Gotsu General Hospital, Gotsu,
Shimane, Japan

E-mail addresses
Shigeo Maruyama: shigemaru@hotmail.co.jp
Masahiko Koda: masakoda@med.tottori-u.ac.jp
Nobuyuki Oyake: mk25911019@yahoo.co.jp
Hidetoshi Sato: sato-i.c.izumo@salsa.ocn.ne.jp
Yasuyoshi Fujii: yfujii@ig8.so-net.ne.jp
Yutaka Horie: y-horie@saiseikai-gotsu.jp
Yoshikazu Murawaki: murawaki@grape.med.tottori-u.ac.jp

Electronic word count: 3573
Number of figures: 3
Number of tables: 2
List of abbreviations
hepatitis C virus (HCV)
electrocardiography (ECG)
severity score (SS)
interferon (IFN)
indocyanine green (ICG)
sustained virologic response (SVR)
dilated cardiomyopathy (DCM)
histology activity index (HAI)
alanine aminotransferase (ALT)
everse transcriptase-polymerase chain reaction (RT-PCR)
left ventricular end diastolic dimension (LVDd)
left ventricular ejection fraction (LVEF)
single photon emission computed tomography (SPECT)
no virological response (NVR)
prothrombin time (PT)
creatine phosphokinase (CPK)
lactic dehydrogenase (LDH)
brain natriuretic peptide (BNP)
human atrial natriuretic polypeptide (HANP)

Conflict of interest: the authors declare that they have no conflict of interest.

Address correspondence to:
Masahiko Koda
Second Department of Internal Medicine, Faculty of Medicine, Tottori University,
Yonago, Japan
36-1 Nishi-machi, Yonago city, Tottori 683-8504, Japan
Telephone: +81-859-38-6527
Fax: +81-859-38-6529
E-mail: masakoda@med.tottori-u.ac.jp
Abstract

Background & Aims  The existence of a direct pathogenic link between hepatitis C virus (HCV) infection and myocardial injury has not been confirmed. We investigated the association between myocardial conditions and HCV in patients with HCV-related chronic hepatitis using thallium-201 myocardial scintigraphy.

Methods  In 217 consecutive cases of chronic HCV infection without overt heart disease, we performed electrocardiography (ECG), echocardiography, serum tests on myocardial injury and thallium-201 myocardial scintigraphy. Myocardial injury was confirmed by severity score (SS), which was calculated as the sum of thallium-201 perfusion defect scores. SS was followed prior to and after interferon (IFN) therapy in 200 patients with chronic hepatitis C.

Results  An abnormal ECG was found in 9% of the patients with chronic hepatitis C. Abnormal SS was found in 87% of chronic hepatitis C patients. Independent factors related to higher pretreatment SS were histology activity index score, serum HCV RNA titer and indocyanine green disappearance rate. After IFN therapy, SS was improved in patients with sustained virologic response. Among relapsers, the SS improved at the initial disappearance of HCV RNA, but SS worsened with reappearance of HCV RNA. The SS in non-viral responders did not change with IFN therapy.

Conclusions  Myocardial perfusion defects were found in 87% of the patients with
chronic hepatitis C and improved with viral eradication from IFN therapy.

Key words: HCV, interferon, myocardium, thallium myocardial SPECT
Introduction

There are many recent reports of extrahepatic manifestations of hepatitis C virus (HCV) infection in a variety of tissues and organs, including the myocardium [1, 2]. The myocardium may be the target of several types of viral infections. Viral myocarditis is caused by a range of viruses including enteroviruses (particularly Coxsackie B virus), adenoviruses, influenza, human immunodeficiency virus and cytomegalovirus; dilated cardiomyopathy (DCM) may be a long-term sequela of viral heart disease in some patients [3-6]. Although enteroviruses are considered the most common pathogens responsible for viral myocarditis [6, 7], preliminary reports suggest that HCV infection may be associated with several myocardial diseases, including DCM [8-10]. However, there is still no evidence that HCV directly causes myocardial injury, and the prevalence of cardiomyopathy in patients with chronic HCV infection is unknown. We evaluated myocardial condition by examining routine cardiac function and thallium-201 myocardial perfusion imaging in 217 biopsy-proven cases of chronic HCV infection and examined the effect of IFN therapy on myocardial injury from infection.
Patients and Methods

Between January 1996 and December 2006, 217 consecutive patients with chronic HCV infection (104 men and 113 women; mean age ± standard deviation [SD], 57 ± 9 years; range, 29-73 years) who were being treated at our hospital were enrolled in this study after giving informed consent. Patients with other causes of chronic liver disease such as autoimmune hepatitis, primary biliary cirrhosis, alcohol abuse (alcohol consumption of more than 20g per day for longer than 5 years) and drug use were excluded. All patients abstained from alcohol entirely during the therapy and follow-up period. None of the patients had overt ischemic or valvular heart disease, as confirmed by electrocardiograph (ECG) exercise stress testing and echocardiography.

The study was approved by the Ethics Committee of our institute. The nature of the study was fully explained to the patients, and informed consent was obtained.

The diagnosis of chronic hepatitis was based on liver biopsy, and was evaluated histologically by the histology activity index (HAI) [11]. Cirrhotic patients were excluded from the present study. Most patients had elevated serum alanine aminotransferase (ALT) levels. The diagnosis of chronic HCV infection was made on the basis of positivity for serum HCV RNA. HCV- RNA level was measured quantitatively by PCR (Cobas Amplicor HCV monitor, Roche). The lower limit of the assay was 1.0 KIU/ml. Samples collected during and after therapy that had undetectable levels of HCV-RNA were checked also by qualitative PCR (Amplicor...
HCV, Roche), which has a higher sensitivity than quantitative analysis, and the results were labeled as positive or negative. The lower limit of the assay was 50 IU/ml.

Routine laboratory tests were performed within 2 weeks before and just after and 6 months after IFN therapy with the automated methods. Serum brain natriuretic peptide (BNP) (normal range; less than 18.4 pg/ml) and human atrial natriuretic peptide (HANP) (normal range; less than 43.0 pg/ml) with an immunoradiometric assay (Shiono-RIA BNP kit, Shiono-RIA ANP kit, Shionogi Co.Ltd, Osaka Japan). Serum γ-globulin fraction was determined by electrophoretic analysis. The disappearance rate of the indocyanine green (ICG) (normal range; 0.158-0.232) was performed in the early morning after overnight fast and was measured by blood samples taken at before, 5, 10 and 15 minutes after injecting 0.5mg of ICG per kg body weight.

Cardiac function was examined by echocardiography in all patients. M-mode echocardiograms were recorded with a Toshiba SSH-140A ultrasound unit equipped with a 3.75 MHz transducer (Toshiba Medical Systems Corporation, Tochigi, Japan) to measure left ventricular end diastolic dimension (LVDd) and left ventricular ejection fraction (LVEF). Thallium-201 myocardial single photon emission computed tomography (SPECT) was used to assess myocardial perfusion defects. Following an overnight fast, thallium myocardial SPECT was carried out 20 minutes after a injection of 111MBq of thallium-201. Data were collected by a rotating gamma camera (GCA-602A/HG, Toshiba Medical Systems Corporation, Tochigi, Japan)
equipped with a low-energy, high-resolution, parallel-hole collimator and a computer analyzer (GMS-5500A, Toshiba Medical Systems Corporation, Tochigi, Japan).

Forty-four planar acquisitions were obtained at 30-second intervals over a 180-degree arc. The photo-window was set at 160KeV±20% for thallium-201. Transverse images covering the left ventricular myocardium were reconstructed with a filtered back-projection algorithm. These images were further processed to obtain vertical long-axial, and horizontal long- and short-axial slices.

Thallium-201 perfusion images were interpreted semiquantitatively using a polar scoring system [12, 13]. Each short-axial slice was divided into 8 segments. The long-axial slice was used for assessment of the apex. There were 17 segments for each patient. Using a color-coded scale, thallium-201 uptake in each segment was scored semiquantitatively with the following four-point grading system; 0=normal perfusion; 1=slight impairment of perfusion (>25% of max cardiac count); 2=moderate impairment of perfusion (>background); 3=no perfusion. Scintigraphic images were interpreted independently by two experienced examiners without knowledge of the clinical findings. Discrepancies between the two readers were resolved by discussion to reach consensus. The total severity score (SS) was calculated as the sum of all defect scores. The mean point of SS in the healthy subjects was 1.2 ± 0.7 (range, 0-2).

Thus, an SS of 3 points or more was defined as abnormal.
Eradication of hepatitis C virus

IFN was administered to 217 patients, of whom 200 completed 24 or 48 weeks of treatment and 6 months of follow-up. Two of 217 patients were early dropouts related to severe side effects of IFN (depression) and five were dropouts because of severe general fatigue and loss of appetite. Five patients discontinued treatment for anemia, three for neutropenia, and two for thrombocytopenia. The first group of patients with chronic HCV infection being treated at our hospital between January 1996 and December 2001 received 5 million units (MU) of natural IFN-α (OIF®, Otsuka Pharmaceutical Co., Osaka, Japan) (n=52) or 6 MU of natural IFN-α (Sumiferon®, Sumitomo Pharmaceutical Co., Osaka, Japan) (n=48) by subcutaneous injection daily for 2 weeks, followed by three injections per week for 22 weeks, for a total dosage of 423-430 MU. The second group, treated between January 2002 and December 2005, received 3 MU of IFNα-2b (IntronA®, Schering Corp., Kenilworth, NJ, USA) subcutaneously three times per week, plus ribavirin (Rebetol®, Schering Corp., Kenilworth, NJ, USA) 600-1000 mg/d orally, both for 24 (n=32) or 48 weeks (n=25). The third group, treated between January 2004 and December 2006, received peginterferon (peg-IFN) α-2b (Pegintron®, Schering Corp., Kenilworth, NJ, USA) at a dose of 1.5 μg/kg subcutaneously each week, plus oral ribavirin at dose of 600-1000mg/d for 24 (n=23) or 48 weeks (n=20). Patients were considered to have sustained viral response (SVR) when HCV RNA was undetectable for 6 months after
the end of therapy. Relapse was defined as undetectable HCV RNA during treatment, followed by detectable HCV RNA after therapy was stopped. All other patients were considered to show no virological response (NVR). Biochemical, hematologic and virological tests were performed at least every 2 weeks. ECG, echocardiography and myocardial perfusion imaging were performed at the same day within 2 weeks before IFN therapy, within 2 weeks after the completion of IFN therapy and 6 months after IFN therapy.

**Statistical analysis**

All measurements are expressed as the mean ± SD. Standard statistical methods were employed, using the Student's *t* test. Differences between the control group and chronic infection group were determined using analysis of variance (ANOVA). Correlation analysis was carried out by univariate linear regression analysis. Multivariate forward stepwise regression analysis to identify independent factors for SS by thallium-201 perfusion image was conducted by Stat View version 5.0 (SAS Institute Inc. 1998, North Carolina). A repeated measures analysis of variance and Bonferroni’s multiple comparison test were used to determine differences in SS between IFN response groups (SVR, Relapse and NVR) and SS changes over time. P<0.05 was considered statistically significant.
Results

Table 1 shows clinical characteristics patients with chronic hepatitis C. One hundred twenty-four patients with chronic HCV infection were infected with genotype 1b, 60 with type 2a, and 33 with type 2b. Mean HCV RNA titer was 2.42 ± 0.84 (log10 copies/mL).

An abnormal ECG was found in 20 patients (9%) with chronic hepatitis C: fifteen patients had sinus bradycardia and five had incomplete right bundle branch block before IFN therapy. LVDd and LVEF were normal in these patients, all of whom had no signs and/or symptoms of heart disease.

The incidence of abnormal SS (≥3) was 87% for the chronic hepatitis C patients. The frequency of abnormal SS was not significantly different between patients treated with IFN monotherapy and those treated with IFN and ribavirin combination therapy. SS in patients with genotype 1b was significantly higher than that in patients with genotype 2a (4.5 ± 1.7 vs. 2a: 3.7 ± 1.5, respectively; P=0.0062), but not in patients with genotype 2b (4.6 ± 2.0, p=0.346).

Pretreatment SS showed significant correlation with serum ALT, γ-globulin, ICG disappearance rate, serum HCV RNA titer and HAI score, but not with age, total bilirubin or prothrombin percent activity (Table 2). Multiple linear regression was performed to explore determinants of pretreatment SS. Plausible predictors (HAI score, serum HCV RNA titer, ALT, γ-globulin and ICG disappearance rate) were
included in this model and analyzed by forward stepwise regression. The final linear regression model identified HAI score, serum HCV RNA titer and ICG disappearance rate as significant independent predictors (|R|=0.778; R²=0.605; P<0.0001).

Two hundred patients with chronic HCV infection completed IFN therapy, among whom SVR was observed in 92 patients (46.0%), relapse in 57 (28.5%), and NVR in 51 (25.5%). Figure 1 shows the changes in SS before and after IFN therapy for 24 weeks in patients with chronic hepatitis C. One hundred patients received IFN monotherapy, 32 combined IFNα-2b and ribavirin therapy, and 23 combined peg-IFNα-2b and ribavirin therapy [62 (40.0%), 48 (31.0%), and 45 (29.0%) patients had SVR, relapse, or NVR, respectively].

There was a significant interaction between IFN response groups and SS changes over time (among 3 groups; p<0.0001, SVR group vs Relapse group; p=0.0036, SVR group vs NVR group; p<0.0001, Relapse group vs NVR group; p<0.0001 by Bonferroni’s multiple comparison test). SS in 57 patients (92.4%) of the SVR group was improved at the end of IFN therapy and remained in the normal range for 6 months after completion of therapy. In patients with SVR, SS was significantly reduced at the end of IFN therapy and for 6 months after therapy (P<0.01) compared to baseline and there was no significant difference between the SS at these two timepoints. The SS in the relapse group was improved at the end of IFN therapy, but returned to the baseline at 6 months after completion of IFN therapy. SS in 42 patients
(93.3%) of the NVR group was abnormal at all time points. SS values were not significantly different among the three time points.

Figure 2 shows the changes in SS before and after combined therapy with IFN (IFNα-2b or peg-IFNα-2b) and ribavirin for 48 weeks in patients with chronic HCV infection. Twenty-five patients received IFNα-2b plus ribavirin and 20 peg-IFNα-2b plus ribavirin (30, 9, and 6 patients achieved SVR, relapsed, or had NVR, respectively). The changes in SS in patients treated with IFN combination therapy for 48 weeks were almost the same as those in patients treated for 24 weeks. There was a significant interaction between IFN response groups and SS changes over time (among 3 groups; p<0.0001, SVR group vs Relapse group; p=0.0467, SVR group vs NVR group; p=0.035, Relapse group vs NVR group; p=0.2382 by Bonferroni’s multiple comparison test).

Figure 3 shows typical myocardial SPECT images processed to obtain short-axis and vertical long-axis sections in the SVR, relapse and NVR groups that received IFN monotherapy for 24 weeks. In the SVR group, the uptake of thallium-201 was decreased in the anterior, inferior, posterior and apical segments, and SS was 5 points prior to IFN therapy. At the completion of IFN therapy, the uptake was almost normal and SS was 1 point, and this continued for 6 months after the completion of IFN therapy. In the relapse group, the uptake of thallium-201 was decreased in the anterior, inferior and apical segments and SS was 6 points prior to IFN therapy. At the
completion of IFN therapy uptake was almost normal and SS was 2 points, but 6
months after therapy, SS increased again to 5 points. In the NVR group, SS remained
high points in all three periods. In patients who received IFN (IFNα-2b or
peg-IFNα-2b) and ribavirin combination therapy for 24 or 48 weeks, the uptake of
thallium-201 showed almost the same changes as in patients who received IFN
monotherapy for 24 weeks (not shown).
Discussion

The present study indicated that the prevalence of myocardial injury in patients with chronic hepatitis C was 87%. Matsumori et al [8] first reported that the prevalence of HCV among DCM patients was significantly higher than among controls (16.7% vs. 2.5%) and hypothesized the existence of a pathogenic link between HCV infection and genesis of DCM. However, in the present study an abnormal ECG was found in only 20 patients (9%), none of whom exhibited clinical signs and symptoms of heart disease. Myocardial perfusion imaging using thallium-201 permits noninvasive detection of coronary artery disease and myocardial conditions [13]. The main factors that determine myocardial uptake of thallium are myocardial perfusion and cell viability. In 19 patients with infectious myocarditis who had normal exercise tests, four patients showed myocardial perfusion defects [14], suggesting that thallium scintigraphy was the most sensitive test to detect myocardial injury. Our observation also confirmed that 189 patients with chronic HCV infection with myocardial perfusion defects had no evidence of clinical myocarditis. Patients with chronic HCV infection might have extremely mild cardiomyopathy as an extrahepatic manifestation of their infection, but which is not clinically overt.

The mechanisms by which HCV damages the myocardium have not been elucidated. We examined independent factors among clinicopathologic parameters for SS abnormality, and found that HAI score, HCV RNA and ICG disappearance rate
were independent factors; these all reflect severity of liver disease and HCV infection.

ICG disappearance rate represents hepatic parenchymal function and circulatory impairment, that is, hyperdynamic circulation. Hyperdynamic circulation in patients with cirrhosis or portal hypertension may influence on myocardial perfusion. However, because the present study did not enroll cirrhotic patients, circulatory abnormality due to cirrhosis was hardly considered to affect myocardial perfusion.

Next, we examined the effects of IFN therapy on myocardial injury associated with chronic HCV infection. In 149 patients (92 and 57 with SVR and relapse, respectively) of a total of 200 patients with chronic HCV infection, myocardial perfusion had normalized by the completion of IFN therapy: all were negative for serum HCV RNA. Patients achieving SVR had normal myocardial perfusion imaging at the end of and 6 months after therapy. Patients with relapse also had normal myocardial perfusion imaging at the end of IFN therapy, but had abnormal imaging at 6 months after therapy. Patients with NVR had abnormal imaging throughout. These results indicated that HCV itself caused myocardial injury.

Indeed, another report has indicated that HCV replicates in the myocardium, as evidenced by the isolation of negative strands of the virus, which constitute replicable intermediates of HCV [15]. Recent evidence has suggested that HCV core protein directly damages the myocardium [16]. Based on these results, we speculated that a direct cytopathic effect of HCV on myocardium could play a major role in myocardial
injury.

The present study has several limitations. First, we could not perform the myocardial biopsy for confirmation of HCV viral load within the myocardium and for obtaining the histological findings. However, a few studies have demonstrated HCV RNA in myocardium of myocarditis or dilated cardiomyopathy in patients with HCV infection [15, 17]. Furthermore, because the myocardial biopsies were not performed before and after IFN therapy, we could not confirm that the eradication of HCV causes the improvement of the perfusion defect. Second, the accurate pathophysiology and mechanism of myocardial injury due to HCV are still unknown. The uptake of Thallium 201 by myocardium occurs by both passive diffusion and active mechanism involving the potassium pump, resulting in a first-pass extraction of 88% by myocardium [13]. The two possibilities are considered as the mechanisms of myocardial perfusion defect due to HCV. One is that HCV affects potassium that HCV affects endothelium, resulting in attenuation of blood flow. Further basic research is needed to resolve this problem. This injury appears to be reversible by IFN therapy and no myocardial dysfunction on the echocardiogram suggests that these patients were at most mildly affected by the virus. Third, we did not check the infection of other viruses, which occur myocardial injury, such as coxsachie B, adenovirus, influenza virus, HIV and enterovirus [18, 19]. The replication of these viruses is reported to also be inhibited by IFN [20].
In conclusion, our study is the first to demonstrate a relationship between chronic HCV infection and myocardial perfusion defects in a large number of patients. Although further studies are required to evaluate the exact relationship between chronic HCV infection and myocardial injury, our study suggests that HCV infection may play an important causal role in the pathogenesis of myocardial injury.
References


Figure legend

Fig. 1. The Changes in the severity score of myocardial perfusion defects in the
SVR, relapse and NVR groups after IFN therapy for 24 weeks.

The dotted lines indicate the normal range. Significances of individual differences
were evaluated by using Bonferroni’s multiple comparison test.

Fig. 2. The Changes in the severity score of myocardial perfusion defects in the
SVR, relapse and NVR groups after the combination therapy of IFN and
ribavirin for 48 weeks.

The dotted lines indicate the normal range. Significances of individual differences
were evaluated by using Bonferroni’s multiple comparison test.

Fig. 3. Typical myocardial SPECT images

Typical myocardial SPECT images processed to obtain short-axis (left) and vertical
long-axis (right) sections in the SVR, relapse, and NVR groups before IFN therapy
(0M; A), at the completion of IFN therapy (6M; B) and 6 months after the completion
of IFN therapy (12M; C). The arrows show the parts of myocardial perfusion defects.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chronic hepatitis C (n=217)</th>
<th>Normal range</th>
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<tr>
<td>Age (yr)</td>
<td>57 ± 9</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>104/113</td>
<td></td>
</tr>
<tr>
<td><strong>Liver function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.7 ± 0.3</td>
<td>0.2-1.0</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>77 ± 61</td>
<td>5-45</td>
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<tr>
<td>γ-globulin (g/dl)</td>
<td>1.6 ± 0.3</td>
<td>0.7-1.2</td>
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<tr>
<td>Prothrombin percent activity (%)</td>
<td>90 ± 16</td>
<td>80-100</td>
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<tr>
<td>ICG disappearance rate (%)</td>
<td>0.172 ± 0.041</td>
<td>0.158-0.232</td>
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<tr>
<td><strong>HAI score</strong></td>
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<tr>
<td>HAI (point)</td>
<td>8.9 ± 3.3</td>
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<td><strong>Cardiac function</strong></td>
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<td>Abnormal ECG (%)</td>
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<tr>
<td>CPK (IU/L)</td>
<td>94 ± 46</td>
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<tr>
<td>LDH (IU/L)</td>
<td>172 ± 38</td>
<td>107-230</td>
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<td>BNP (pg/ml)</td>
<td>22.0 ± 18.8</td>
<td>less than 18.4</td>
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<tr>
<td>HANP (pg/ml)</td>
<td>19.6 ± 12.5</td>
<td>less than 43.0</td>
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<td>LVDd (mm)</td>
<td>48 ± 5</td>
<td>39-55</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>66 ± 7</td>
<td>55-80</td>
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<tr>
<td>severity score (%)</td>
<td>4.3 ± 1.6</td>
<td>less than 3</td>
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<tr>
<td>severity score ≥3 (%)</td>
<td>87</td>
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HAI: histology activity index, BNP: brain natriuretic peptide, HANP: human atrial natriuretic peptide, LVDd: left ventricular end diastolic dimension,
Table 2. Correlations between pre-treatment severity score (SS) points and clinical biochemical parameters

<table>
<thead>
<tr>
<th>parameters</th>
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<tr>
<td>Age</td>
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<td>Bilirubin (mg/dl)</td>
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<td>ALT (IU/L)</td>
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<td>γ-globulin (g/dl)</td>
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<td>Prothrombin percent activity (%)</td>
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<td>ICG disappearance rate</td>
<td>-0.181</td>
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<td>HCV RNA (KIU/ml)</td>
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<tr>
<td>HAI score</td>
<td>0.737</td>
<td>&lt;0.0001</td>
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Figure 1
Figure 2
Figure 3