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# Thrombocytopenia represents a risk for deterioration of liver function after radiofrequency ablation in patients with hepatocellular carcinoma

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**Background/Aims:** We evaluated changes in liver function parameters and risk factors for the deterioration of liver function 12 months after percutaneous radiofrequency ablation (RFA) therapy in patients with hepatocellular carcinoma (HCC).

**Methods:** The subjects in this retrospective study comprised 102 patients with HCC who had undergone RFA therapy and exhibited no recurrence of HCC 12 months thereafter. Serial changes in serum total bilirubin and albumin, prothrombin time, and Child-Pugh score were evaluated before RFA and 3, 6, 9, and 12 months thereafter. Deterioration of liver function was defined when the Child-Pugh score increased by at least 2 at 12 months after RFA therapy. We determined the factors related to aggravation of liver function after RFA therapy.

**Results:** Liver function had deteriorated 12 months after RFA in 29 patients (28.4%). Serum albumin levels decreased significantly from before (3.7±0.1 g/dL, mean±SD) to 12 months after RFA therapy (3.3±0.1 g/dL, $P$=0.002). The Child-Pugh score increased significantly during the same time period (from 6.1±0.2 to 7.2±0.3, $P$<0.001). Pre-RFA thrombocytopenia (≤100,000/mm$^3$) was revealed as a significant risk factor for the deterioration of liver function after RFA. However, no patients had episodes of bleeding as a complication of RFA.

**Conclusions:** Among the liver-function parameters, serum albumin level was markedly decreased in HCC patients over the course of 24 months after RFA therapy. A pre-RFA thrombocytopenia represents a major risk factor for the deterioration of liver function. **(Clin Mol Hepatol 2012;18:302-308)**

**Keywords:** Radiofrequency ablation; Thrombocytopenia, Liver function

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with an increasing number of patients.[1,2] Surgical treatment is curative treatment method for HCC if the tumor is single in non-cirrhotic liver.[3] However only 10% to 37% of the patients are eligible for surgical resection because of multiple tumors in both lobes, location of the tumor to major vascular and biliary structures precluding margin-negative surgical resection, advanced stage on presentation, or poor liver function reservoir due to the underlying liver disease.[4-6] Liver transplantation provides an alternative curative treatment for small unresectable

**Abbreviations:**

AFP, alpha fetoprotein; AIH, autoimmune hepatitis; ALT, alanine aminotrasferase; BCAA, branched-chain amino acid; CT, computed tomogram; HCC, hepatocellular carcinoma; IL, interleukin; PEI, percutaneous ethanol injection; PT, prothrombin time; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

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HCC,[7,8] but a shortage of liver grafts limits the applicability of this approach. Radiofrequency ablation (RFA) is a minimally invasive technique as a curative treatment modality for HCC. It is well-tolerated in HCC patients with advanced cirrhosis, with low morbidity rate ranging from 0% to 28% and peri-operative mortality rate of 0% to 2%.[9,10] A recent randomized controlled trial also suggested that percutaneous RFA was as effective as hepatic resection in terms of overall survivals in selected patients.[11] Despite its technical simplicity and safety, deterioration of liver function is inevitable after RFA.[12] Furthermore, the recurrence rate of HCC after RFA is not negligible ranging from 49% to 74% in 5 years.[13,14] Thus, maintaining residual liver function reservoir is very important to treat recurrent HCC appropriately. Although RFA is widely performed in clinical practice, there is little knowledge in changes of residual liver function in patients after RFA. In this study, we evaluated changes in liver function parameters after RFA therapy and identified risk factors for aggravation of liver function.

## PATIENTS AND METHODS

### Patients

Between January 2005 and December 2008, 651 patients with HCC were treated in Kyungpook National University Hospital. Of those patients, we included 102 patients diagnosed as HCC with underlying cirrhosis, who had complete ablation without recurrence for 12 months after RFA, and did not receive any other therapies such as surgical resection, transarterial chemoembolization (TACE) and radiotherapy. Exclusion criteria included patients with previous treatment for HCC, follow-up loss after RFA, and any therapies which can influence liver function parameters such as albumin infusion and therapeutic paracentesis. Anti-viral therapies in patients with chronic hepatitis B were permitted. Patients who had abnormal liver function test due to drug resistance excluded.

Diagnosis of liver cirrhosis were made by either presence of esophageal varix, or radiologic evidences of cirrhosis including surface nodularity and splenomegaly. Diagnosis of HCC was based on the American Association for the Study of Liver Diseases practice guidelines on the management of HCC in 2005.

### Techniques of RFA

Cool-tip™ Radiofrequency Ablation system (Valleylab, USA) was used for RFA. The ablation was performed using an automatic impedance control mode in which the current output was automatically adjusted according to the impedance at the needle tip. For large tumors, multiple overlapping ablations were performed. All ablations aimed at achieving ablation of 1 cm margin of non-tumorous liver parenchyma in a single RFA session.

### Data collection and follow up

Clinical data and treatment outcomes of all patients were retrospectively collected in a computerized database. The treatment protocol and data collection were approved by the institutional review board. To confirm complete ablation, abdominal dynamic computed tomogram (CT) scan was performed 1 month after RFA. All patients underwent serial monitoring of alpha-fetoprotein (AFP) and dynamic CT scan at 3 month intervals for detection of local recurrence, distal intrahepatic recurrence and extrahepatic metastasis. Liver function test along with complete blood count test and prothrombin time (PT), were measured and Child–Pugh score was calculated before RFA and 1, 3, 6, 12 months after RFA therapy.

### Analysis of risk factors for aggravation of liver function

Deterioration of liver function after RFA therapy was defined as an increase in Child-Pugh score by 2 or more at 12 months after RFA therapy. Patients with deteriorated liver function and those with well-preserved liver function after RFA were compared in relation to 16 clinical variables that potentially represent changes of liver function. These included 11 host-related factors (gender, age, hepatitis B surface antigen status, hepatitis C antibody status, Child–Pugh classification, Child-Pugh score, pre-RFA albumin, pre-RFA total bilirubin, pre-RFA platelet count, pre-RFA alanine aminotrasferase (ALT), pre-RFA PT), and 5 tumor-related factors (pre-RFA AFP, size of tumor, number of tumor, ablation time, number of ablation).

### Statistics

Laboratory data are shown as mean±standard error and range. Comparison of variables after RFA (3, 6, 12 months) was performed using the repeated measured ANOVA. Risk factors for deterioration of liver function were analyzed by Cox proportional hazards regression model. Parameters identified as significant in univariate analysis were tested in the multivariate analysis. $P<0.05$ was considered to be significant. Data processing and analysis

were performed by commercially available software (PASW ver. 18.0 for Windows, Chicago, USA).

## RESULTS

### Baseline characteristics

Demographic data of patient at the time of RFA are shown in Table 1. A total of 102 patients (44 male and 11 female) were included in present study. The median age was 59 years old (ranging from 40 to 88). The majority of patients had either chronic hepatitis B or hepatitis C for underlying disease. The size of the tumor was 2.5±0.1 cm (1.0-5.6 cm) in diameter. Seventy six patients (74.5%) had solitary HCC whereas 2 patients (2.0%) had 4 nodules in liver. Serum level of AFP was 186.9±69.8 ng/mL (0.9-7025 ng/mL). Ablation was performed in single cycle in 32 patients (31.4%) and multiple overlapping ablations were performed in 70 patients (68.6%). Total ablation time was 21.9±1.5 minutes (6-48 minutes). Based on Child-Pugh classification, 66 patients (64.7%) were in Child A and 36 patients (35.3%) in Child B. Ascites was observed in 14 patients (13.7%). Laboratory tests performed before RFA procedure were as follows: pre-RFA platelet count 116.6±5.5×$10^3$/$mm^3$ (50-307×$10^3$/$mm^3$), pre-RFA PT 13.2±0.2 seconds (10.6-22.2 seconds), pre-RFA albumin 3.7±0.1 g/dL (2.1-5.1 g/dL), pre-RFA total bilirubin 1.4±0.2 mg/dL (0.4-2.8 mg/dL), and pre-RFA ALT 34.5±3.7 IU/L (6-170 IU/L).

### Serial changes in liver function after RFA therapy

Child-Pugh score was significantly increased from 6.1±0.1 before RFA to 7.0±0.1 in 6 months and 7.2±0.2 in 12 months after RFA ($P$<0.001). Serum albumin level decreased significantly after RFA therapy from 3.7±0.7 g/dL before RFA to 3.5±0.1 g/dL in 6 months ($P$=0.002). Serial changes in liver function parameters are showed in Figure 1. There was no significant difference in the level of serum total bilirubin, PT levels and platelet counts after RFA.

### Risk factors for aggravation of liver function

A total of 29 patients (28.4%) showed decrease of Child-Pugh score by 2 or more compared to pre-RFA Child-Pugh score. Among 29 patients with deterioration of liver function, Child-Pugh score decreased by 2 in 13 patients, by 3 in 10 patients and by 4 in 6 patients. The Cox proportional hazards regression model revealed that Child-Pugh classification (A vs. B), pre-RFA platelet (≤70,000/$mm^3$), pre-RFA albumin (≤3.5 g/dL), and pre-RFA bilirubin (≥1.1 mg/dL) as significant factors associated with deterioration of

**Table 1.** Baseline characteristics of the patients at the time of radiofrequency ablation

| Parameters | N=102 |
|---|---|
| Sex (Male/Female) | 44/11 |
| Age (yr) | 59.3±1.0 (40-88) |
| HBV/HCV/Alcohol/HBV+HCV/NASH/AIH | 64/17/13/2/4/2 (62.7%/16.7%/12.7%/2.0%/3.9%/2.0%) |
| Tumor number (1/2/3/4) | 76/17/7/2 (74.5%/16.7%/6.9%/2.0%) |
| Ablation cycle (single ablation/multiple overlapping) | 32/70 (31.4%/68.6%) |
| Ascites (No/Yes) | 88/14 (86.3%/13.7%) |
| Child-Pugh classification (A/B) | 66/36 (64.7%/35.3%) |
| Size of tumor (cm) | 2.5±0.1 (1.0-5.6) |
| Total ablation time (min) | 21.9±1.5 (6-48) |
| pre-RFA platelet (×$10^3$/$mm^3$) | 116.6±5.5 (50-307) |
| pre-RFA PT (sec) | 13.2±0.2 (10.6-22.2) |
| pre-RFA albumin (g/dL) | 3.7±0.1 (2.1-5.1) |
| pre-RFA bilirubin (mg/dL) | 1.4±0.1 (0.4-2.8) |
| pre-RFA ALT (IU/L) | 34.5±3.7 (6-170) |
| pre-RFA AFP (ng/mL) | 186.0±69.8 (0.9-7075) |
| pre-RFA Child-Pugh score | 6.1±0.1 (5-9) |

HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; AIH, autoimmune hepatitis; RFA, radiofrequency ablation; PT, prothrombin time; ALT, alanine aminotransferase; AFP, alpha-fetoprotein. Data were presented as mean±standard error, minimum-maximum: range.


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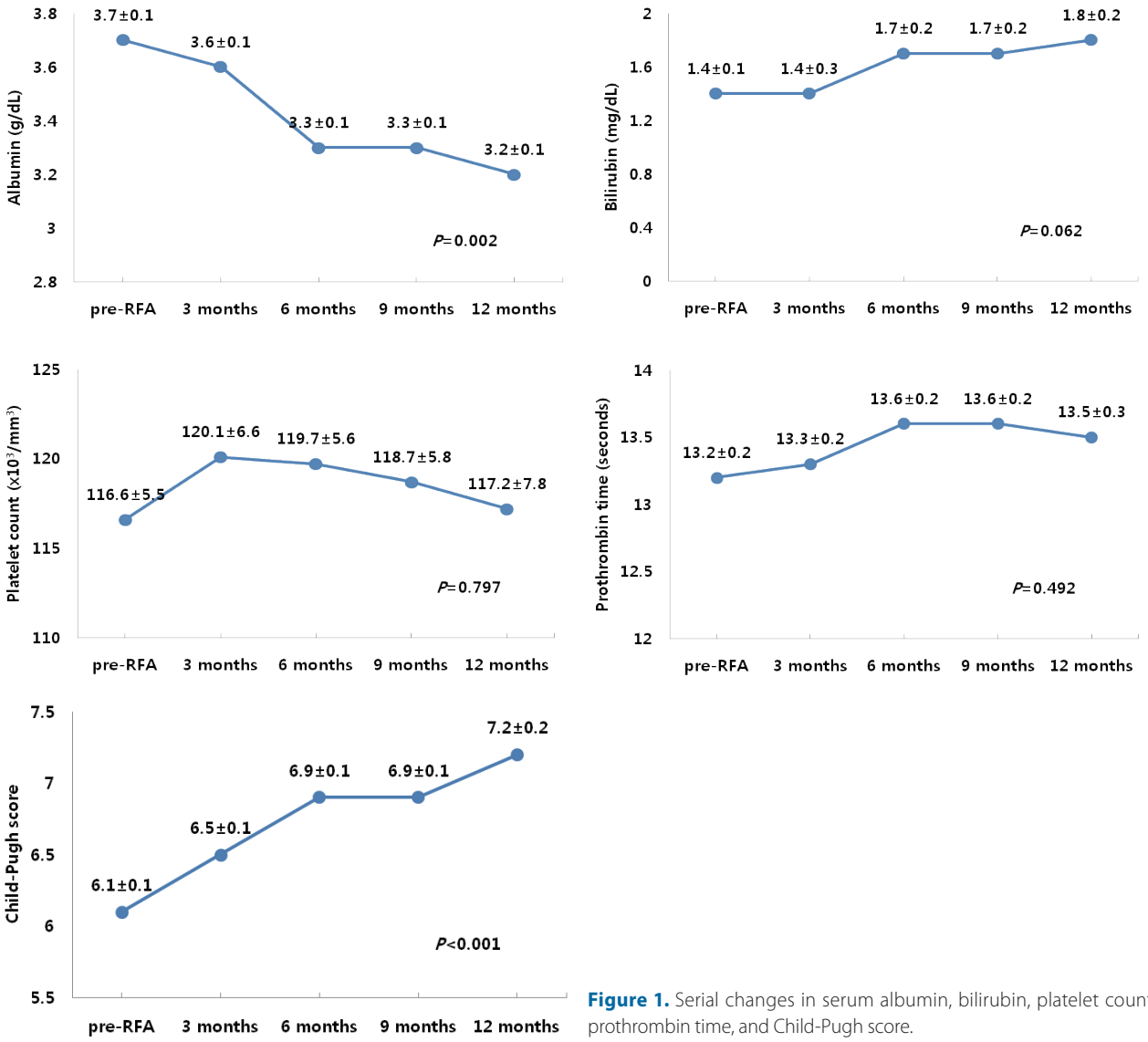


**Figure 1.** Serial changes in serum albumin, bilirubin, platelet count, prothrombin time, and Child-Pugh score.

liver function after RFA therapy. Although the number of tumor, multiple ablation cycles, and advanced cirrhosis with Child-Pugh score more than 8 showed high odds ratio for deterioration of liver function, they failed to be statistically significant. On the other hand, sex, age, the underlying liver disease, presence of ascites, tumor size (≥2 cm), ablation time (≥20 minutes), bilirubin (≥1.1 mg/dL), ALT (≥80 IU/L), and AFP (≥100 mg/mL) were not significantly associated with deterioration of liver function. In multivariate analysis performed with variables with potential risk factors in univariate analysis, pre-RFA platelet count (≤70,000/mm$^3$) was the only significant factor identified as a factor increasing risk for deterioration of liver function (Table 2).

## DISCUSSION

The present study evaluated serial changes in albumin, total bilirubin, PT, platelet count, and Child-Pugh score over the course of 12 months following RFA therapy. We identified risk factors for short term deterioration of liver function after RFA therapy. Our findings demonstrated that albumin significantly decreased and Child-Pugh score significantly increased in 12 months after RFA.

The decrease in serum albumin is considered to be related to three mechanisms. The first is loss of normal liver parenchymal volume after tumor ablation. The second is inhibition of albumin synthesis due to several inflammatory cytokines caused by ablation procedure. The inflammation from heat damage accelerates

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**Table 2.** Risk factors contributing to the deterioration of liver function after radiofrequency ablation

| Univariate analysis | | |
|---|---|---|
| **Variables** | **Odds ratio (95% CI)** | ***P* value** |
| Sex (male) | 1.63 (0.711-3.710) | 0.250 |
| Age (≥75 years) | 1.28 (0.303-5.404) | 0.737 |
| Chronic hepatitis C | 0.04 (0.000-3.450) | 0.155 |
| Chronic hepatitis B | 1.67 (0.459-6.056) | 0.438 |
| Tumor number (single vs. multinodular) | 1.44 (0.942-2.213) | 0.092 |
| Ablation cycle (single vs. multiple) | 2.63 (0.909-7.601) | 0.074 |
| Ascites (yes) | 0.99 (0.528-1.774) | 0.916 |
| Child classification (A vs. B) | 4.35 (1.906-9.946) | <0.001 |
| Tumor size (≥2.0 cm) | 1.07 (0.799-1.419) | 0.667 |
| Ablation time (≥20 min) | 1.05 (0.470-2.327) | 0.913 |
| Child-Pugh score (≥9 points) | 2.35 (0.889-6.202) | 0.085 |
| pre-RFA platelet (≥70,000/mm$^3$) | 3.47 (1.625-7.418) | 0.001 |
| pre-RFA albumin (≥3.5 g/dL) | 5.21 (2.102-12.902) | <0.001 |
| pre-RFA bilirubin (≥1.1 mg/dL) | 3.37 (1.358-8.338) | 0.009 |
| pre-RFA ALT (≥80 IU/L) | 0.94 (0.223-3.969) | 0.933 |
| pre-RFA AFP (≥100 mg/mL) | 1.06 (0.464-2.421) | 0.890 |
| **Stepwise multivariate analysis** | | |
| **Variables** | **Odds ratio (95% CI)** | ***P* value** |
| Tumor number (single vs. multinodular) | 0.91 (0.397-2.102) | 0.832 |
| Ablation cycle (single vs. multiple) | 2.15 (0.721-6.387) | 0.170 |
| Child classification (A vs B) | 1.53 (0.450-5.205) | 0.496 |
| Child-Pugh score (≥9 points) | 1.245 (0.339-2.637) | 0.914 |
| pre-RFA platelet (=70,000/mm$^3$) | 2.92 (1.325-6.430) | 0.008 |
| pre-RFA albumin (=3.5 g/dL) | 3.35 (0.868-12.928) | 0.079 |

RFA, radiofrequency ablation; ALT, alanine aminotransferase; AFP, alpha-fetoprotein.

the production of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and transforming necrosis factor alpha.[15] Such inflammatory cytokines not only stimulate the production of acute phase proteins including C-reactive protein, but also inhibit the synthesis of albumin.[16] Third, serum albumin extravasated from the inflammatory foci. Therefore, both inflammatory response and loss of normal liver volume account for decrease in serum albumin.

Kota et al[17] previously reported that alteration of liver function after percutaneous ethanol injection. The deterioration of the liver function was observed in only 9.6% of patients who underwent PEI or the combination of PEI and TACE. On the contrary, 34% of patients who underwent RFA or the combination of RFA and TAE showed deterioration of liver function. In present study, the deterioration of liver function was observed in 29 patients (28.4%). Although the present study did not compare the changes of liver function with control arms, the deterioration of liver function could be resulted from RFA procedure, not from progression of underlying liver disease.[18]

The platelet counts of patients ranged from 50,000/mm$^3$ to 30,7000/mm$^3$ and patients with platelet count less than 100,000/mm$^3$ were 45 (44.1%). Although platelet was transfused only in 5 patients with thrombocytopenia less than 60,000/mm$^3$, there were no cases of bleeding as complication after RFA. Thrombocytopenia is common in patients with chronic liver disease, reported in as many as 76% of cirrhotic patients.[19] Among these cirrhotic patients, platelet count below 50,000/mm$^3$ is observed in 1% of patients and this condition can significantly increase the risk of spontaneous bleeding such as cerebral hemorrhage or hemorrhage from gastrointestinal sources.[20,21] Many physicians require platelet counts of ≥80,000/mm$^3$ to perform percutaneous liver


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biopsy safely, but several reports suggest that the invasive procedures including liver biopsy might be performed in patients with platelet counts ≥50,000/mm$^3$ with little risk of bleeding.[22-24]

In this study, multivariate analysis identified platelet count below 70,000/mm$^3$ as a major risk factor for deterioration of liver function following RFA. The possible causes of thrombocytopenia include splenic sequestration of platelets, suppression of platelet production in the bone marrow and decreased activity of the hematopoietic growth factor, thrombopoietin. In general, thrombocytopenia is considered to be a secondary phenomenon caused by progression of liver cirrhosis. However, Kodama et al[25] reported that thrombocytopenia per se affected liver cirrhosis in mice model. In addition to the fact that liver cirrhosis progresses in parallel with the decrease of platelet count, several studies on human patients have shown that splenectomy or partial splenic embolization can improve the liver function of cirrhotic patients in parallel with elevation of platelet count.[26,27]

This study has several limitations. First, nutritional factor was not considered as a potential factor for deterioration of liver function. Patients with advanced cirrhosis and malnutrition are well known to exhibit poor prognosis.[28] Muto et al[29] have shown that oral administration of branched-chain amino acid (BCAA) can improve nutritional status and event-free survival in cirrhosis. Future studies can focus on the role of BCAA granules and BCAA-enriched nutrients in cirrhosis patients in a nutritional aspect. Second, generalization cannot be made from a small number of patients from a single center. Therefore, further clinical study is important in order to elucidate whether an increase in platelet count is beneficial for preventing the deterioration of liver function after RFA in thrombocytopenic patients with HCC.

In conclusion, serum albumin level gradually decreases over the course of 12 months after RFA in HCC patients. A pre-RFA thrombocytopenia (≤70,000/mm$^3$) represents a critical parameter to predict deterioration of underlying liver cirrhosis in HCC patients after RFA procedure.

## Conflicts of Interest

The authors have no conflicts to disclose.

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