Prognostic Factors of Computed Tomography Findings in Patients with Severe Acute Hepatic Failure Scheduled to Undergo Transcatheter Arterial Steroid Injection Therapy

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Abstract

Purpose: To determine the prognostic factors of transcatheter arterial steroid injection therapy (TASIT) in patients with severe acute hepatic failure, with special reference to computed tomography (CT) findings.

Material and Methods: Fifty-one patients (32 men, 19 women; mean age, 48 years) who underwent TASIT for severe acute hepatic failure at the authors’ institution were enrolled. Based on patient outcomes, the patients were divided into effective and ineffective treatment groups. Attenuation of the liver parenchyma and liver volume were calculated from CT data acquired before TASIT. Miscellaneous CT findings, such as heterogeneous enhancement of the liver parenchyma, periportal edema, ascites, gall bladder wall thickening, lymphadenopathy and splenomegaly, were also evaluated. The data were compared between the groups.

Results: The effective and ineffective treatment groups included 39 and 12 patients, respectively. All patients in the ineffective group were diagnosed with fulminant liver failure. Mean attenuation of the liver parenchyma in all patients was 44.0 Hounsfield units (HU). Mean CT value in the liver parenchyma was higher in the effective (44.7 HU) than in the ineffective (40.1 HU) treatment groups; however, the difference was not statistically significant. Of the 15 patients in whom liver parenchyma CT values were > 45 HU, all responded to TASIT. Mean liver volume and miscellaneous CT findings were not significantly different between the effective and ineffective treatment groups.

Conclusion: Relatively preserved attenuation of the liver parenchyma may be a good prognostic factor for severe acute hepatic failure after TASIT.

Key words: severe acute hepatic failure, fulminant hepatitis, hepatic arterial infusion therapy, Attenuation of liver parenchyma, liver volume

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**Introduction**

Severe acute hepatic failure (SAHF) is a disorder in which liver damage progresses rapidly, and is accompanied by jaundice, ascites, encephalopathy, and/or coagulopathy [1, 2]. In a small proportion of patients with SAHF, the disease is self-limiting. However, it may sometimes progress to the fulminant form of SAHF, which has a high mortality rate [2]. Intravenous steroid injection and plasma exchange, the traditional therapies for SAHF, are often ineffective in such cases [3-5]. Liver transplantation is, therefore, the only effective treatment for patients with the fulminant form of SAHF [6]. It remains difficult to predict disease progression from the non-fulminant to the fulminant form of SAHF. In addition, there are few effective treatments that can prevent the progression of SAHF to the fulminant form.

At our institution, transcatheter arterial steroid injection therapy (TASIT) has been performed in patients with the fulminant and non-fulminant forms of SAHF to prevent rapid progression and irreversibility of liver damage. TASIT is a novel method that efficiently suppresses intrahepatic macrophage activity in damaged livers, and is performed simultaneously with—or subsequent to—plasma exchange and intravenous steroid injection. Better prognoses (i.e., higher survival rate and decreased rate of liver transplantation) have been reported in patients who underwent TASIT than in patients who did not [7]. Moreover, we reported that TASIT is a feasible and efficient treatment option for SAHF, regardless of anatomical variation in the hepatic artery [8].

However, indications of TASIT for SAHF have not yet been clarified. TASIT has been ineffective in some patients with SAHF, who resultedantly underwent liver transplantation or died soon after. Kotoh et al. [9] evaluated various laboratory data from patients with SAHF and suggested that the indication for TASIT could be determined by classifying the degree of macrophage activity in these individuals.

In the present study, we focused on computed tomography (CT) findings from patients with SAHF. Decreased attenuation of the liver parenchyma and a reduction in liver volume have been reported in patients with the fulminant form of SAHF [10, 11]. Moreover, we often observe that decreased attenuation of the liver parenchyma recovers along with improvement in liver function after TASIT. CT findings of SAHF may be useful for predicting the likelihood of positive therapeutic effect of TASIT. The purpose of this study therefore, was to compare various CT findings of patients with SAHF between those in whom TASIT was effective and those in whom it was ineffective, and to assess whether these findings can be useful predictors of the therapeutic effect(s) of TASIT.

**Material and Methods**

**Patients**

Between January 2005 and September 2008, 51 patients with SAHF (32 men, 19 women; mean age, 48 years [range, 18-78 years]) underwent indwelling catheter placement in the hepatic artery, and TASIT was subsequently performed. The causes of SAHF included: viral hepatitis type A (n = 4); viral hepatitis type B (n = 14); drug-induced hepatitis (n = 4); Wilson disease (n = 3); alcoholic hepatitis (n = 3); and unknown origin (n = 21). Laboratory data were as follows: aspartic aminotransferase (AST), 542-20,370 IU/L (median 4735 IU/L); alanine aminotransferase (ALT), 585-12,230 IU/L (median 3593 IU/L); prothrombin time (PT) 10-69% (median 36%). Of the 51 patients with SAHF, 22 (43%) were diagnosed with the fulminant form, having hepatic coma above grade II and a PT value < 40%. As a result, 29 (57%) of the 51 patients were diagnosed with the non-fulminant form of SAHF.

Patients with SAHF, in whom the disease was highly suspected to have progressed to the fulminant form, and patients with fulminant hepatitis were selected as candidates for TASIT. Severe liver atrophy on CT and/or the passage of too much time after onset were determined to be contraindications to TASIT.

The ethics committee of the authors’ institution approved the protocol, and written informed consent was obtained from all patients.

**CT protocol**

Body CT was performed in 49 of the 51 (96.1%) patients before TASIT, immediately after admission or at the onset of SAHF. CT was performed using a 4-row or 64-row multidetector CT scanner (Aquilion, Canon Medical Systems, Ootawara, Japan). Unenhanced CT was performed in 7 patients, both unenhanced and enhanced CT in 32 patients, and enhanced CT in 10 patients. The scanning parameters were as follows: collimation 3 or 0.5 mm; pitch 5.5 or 53; and reconstruction 5 mm. Forty-two patients underwent intravenous administration of 100 ml of iopamidol solution (300 mgI/ml, Iopamiron300; Bayer; Osaka, Japan) or iohexol solution (300 mgI/ml, Omnipaque; Daiichi Pharmaceutical Co., Ltd.; Tokyo, Japan) at a rate of 2.0-3.0 ml/s using a power injector. With or without pre-contrast scanning, dynamic scanning was performed at 45 s, 70 s, and 240 s, or at 70 s and 240 s.

**Catheter placement and TASIT**

Under local anesthesia, an indwelling 3-4 Fr catheter (Medikit, Tokyo, Japan) was placed in the hepatic artery using a transfemoral approach in the angiographic suite. The catheter tip was placed in the common hepatic artery (CHA), proper hepatic artery (PHA), or replaced hepatic artery, where the catheter could be stabilized and the drug...
Table 1. Outcomes of TASIT

| Outcome                 | Number of patients |
|-------------------------|--------------------|
| Effective               | 39 (76)            |
| Discharged              | 39                 |
| Ineffective             | 12 (24)            |
| Liver transplantation   | 3                  |
| Deceased                | 9                  |
| Total                   | 51                 |

Note: Numbers are the total numbers of patients who underwent CT scans before TASIT; numbers in parentheses indicate the percentages of patients.

could be distributed over a wider area of the liver parenchyma.

After the catheter was placed, the patient was kept on bed rest and underwent steroid pulse treatment. One gram of methylprednisolone per day was infused for 2 h via the indwelling catheter using a syringe pump. A total of 3 g of methylprednisolone was administered over a 3-day period. During the periods when drug infusion was not being administered, the catheter system was filled with 3,000 IU of heparin to prevent luminal obstruction. During TASIT, most patients concurrently underwent plasmapheresis.

Assessment

Therapeutic effects were evaluated on the basis of patient outcomes. The effective treatment group comprised patients who were alive and in remission after TASIT, while the ineffective treatment group comprised patients who died or worsened, and underwent liver transplantation after TASIT.

Attenuation of the liver parenchyma and liver volume were also evaluated using unenhanced CT. Regions of interest were delineated on the caudate lobe and left lateral, left medial, right anterior, and right posterior hepatic segments on unenhanced CT to measure CT values of the liver parenchyma. The mean CT values for these measurements were calculated. The volume of the entire liver was measured using CT volumetry and the Aquarius Workstation (TeraRecon, Inc., Foster City, CA), and liver volume per body surface area (BSA) was calculated. Miscellaneous CT findings, such as heterogeneous enhancement of the liver parenchyma, periportal edema, ascites, gall bladder wall thickening, lymphadenopathy and splenomegaly, were evaluated. These values were compared between the effective and ineffective TASIT groups. These three imaging analyses were evaluated by two radiologists (10 and 14 years’ experience).

The Fisher’s exact test was used for statistical analysis of non-parametric factors. Mean CT values of the liver parenchyma and liver volumes per BSA of the two groups were compared using the t-test; P < 0.05 was considered to be statistically significant. JMP (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis.

Results

Percutaneous catheter placement was performed without any complications in all patients, and TASIT was initiated. Thirty-nine (76%) patients responded to TASIT (effective group) and 12 patients (24%) did not (ineffective group). All 12 patients in the ineffective group were diagnosed with fulminant liver failure: 3 underwent liver transplantation, and the remaining 9 died (Table 1).

The mean CT value of liver parenchyma in all patients was 44.0 ± 9.9 Hounsfield units (HU). The mean value in the effective group was 44.7 ± 11.8 HU, higher than that in the ineffective group (40.1 ± 4.7 HU); however, the difference was not statistically significant (P = 0.3 [t-test]) (Figure 1). In all patients in the ineffective group, CT values of the liver were < 45 HU; alternatively, CT values of the liver were < 45 HU only in 14 patients (45.2%) in the effective group (Table 2).

The mean liver volume in the effective group was 790.0 ± 164.8 cm³/BSA, slightly larger than that in the ineffective group (789.2 ± 265.1 cm³/BSA), with no statistical differences between the groups (P = 0.6 [t-test]) (Figure 2).

The frequency of miscellaneous CT findings, such as heterogeneous enhancement of the liver parenchyma, periportal edema, ascites, gall bladder wall thickening, lymphadenopathy and splenomegaly, were not significantly different between the effective and ineffective TASIT groups (Table 3).
Discussion

In this study, we focused on CT findings of SAHF before TASIT to assess whether they can be useful predictors of the therapeutic effects of TASIT. The mean attenuation of the liver parenchyma in patients with SAHF was decreased (44.0 ± 9.9 HU). Generally, attenuation of normal liver parenchyma has been reported to be approximately 60-65 HU [12, 13]. Decreased attenuation of the liver parenchyma has been reported to be one of the characteristic findings of SAHF reflecting necrosis of the liver [10, 11, 14]. Our results were consistent with these previous reports. The mean attenuation of liver parenchyma in the effective group was slightly higher than that in the ineffective group, although no statistically significant difference was observed. However,

| Table 2. Attenuation of the liver parenchyma |
|---------------------------------------------|
| Outcome of TASIT | Attenuation | Total |
| Effective | > 45 HU | <= 45 HU | |
| > 45 HU | 17 | 14 | 31 |
| <= 45 HU | 0 | 8 | 8 |

In all patients in the ineffective group, attenuation of the liver parenchyma was less than 45 HU. Otherwise, attenuation of the liver was less than 45 HU in only 14 patients (45.2%) in the effective group.
TASIT was effective in patients with attenuation values > 45 HU for the liver parenchyma (17 of 31 patients in the effective group), and < 45 HU in all patients in the ineffective group. These results suggested that relatively preserved attenuation of the liver parenchyma may be a good prognostic factor of TASIT for SAHF (Figure 3, 4).

Collectively, these two results suggest that the degree of decreased attenuation in the liver parenchyma correlated with the severity of liver damage and that, in patients with SAHF in the effective group, the number of necrotic cells in the liver was smaller than in the ineffective group. However, in one patient in the effective group (Figure 5), decreased attenuation of the liver parenchyma recovered in 8 days. Although this may be attributed to regenerative nodules that formed after SAHF, as reported previously [10, 14, 15], several factors other than liver cell necrosis may participate in attenuation decrease (i.e., ischemia, fatty infiltration, and edema). Such pathological factors would intricately regulate the CT value of the liver parenchyma with SAHF. Additionally, several recent studies have indicated that activated macrophages in the liver may play a key role in the development of fulminant liver failure [16-19]. Because macrophages are involved in iron metabolism, their activation is likely to affect the amount of iron stored in the liver. Thus, CT attenuation of the liver parenchyma in patients with SAHF may be affected by the level of iron stores in the liver. Relatively preserved attenuation of the liver parenchyma in the effective TASIT group in our results may represent an increase in the amount of iron stored in the liver; further study, however, is necessary to confirm this hypothesis.

There were no statistical differences in liver volume between the effective and ineffective TASIT groups. It was reported that a liver volume < 1,000 mL was indicative of a poor prognosis in patients with acute liver failure [20]. In this study, TASIT was initiated immediately after the onset of SAHF—more specifically, before liver atrophy progressed. Instead, patients exhibiting severe liver atrophy on CT were excluded as a contraindication to TASIT. This may explain why liver volume was not a prognostic factor in this study. Clinically, however, it appears unlikely that any treatment—other than liver transplantation—would be effective in patients with SAHF exhibiting marked liver atrophy on CT.

Heterogeneous enhancement of the liver parenchyma on enhanced CT did not demonstrate any statistical difference between the effective and ineffective TASIT groups. This finding was probably related to various factors, such as...
ischemia, necrosis, regional flow of the hepatic artery or portal vein, and changes in the diffusion rate between the interstitial space and vascular space in the liver parenchyma. With regard to CT findings in patients with fulminant hepatitis, Itai et al. reported post-necrotic scar enhancement [15], and Cakir et al. reported unusual imaging findings of nodular regeneration [14]. Therefore, it may be difficult to simply relate these findings to SAHF outcomes.

There were some limitations to this study, the first of which was the small number of patients and its single-institution design. Second, as mentioned previously, the mechanism underlying the decrease in attenuation of the liver parenchyma of patients with SAHF has not been clearly elucidated. To resolve this problem, it is necessary to compare these CT findings with pathology findings from the liver in patients with SAHF. However, percutaneous liver biopsy of patients with SAHF has a high risk for bleeding for coagulopathy [21]; transjugular liver biopsy should, therefore, be performed [22]. Magnetic resonance imaging (MRI) may provide additional information, such as data regarding edema, fibrosis, the degree of iron deposition and, especially, macrophage activity in the liver of patients with SAHF. Because SAHF must be treated promptly, a relatively long wait for MRI examination may not be justified. Third, cases of hepatic failure are often self-limiting and treated only with conservative therapy. We acknowledge the possibility that such a self-limiting case may have been included in the effective group in this study. Analysis of CT atten-
ation of the liver parenchyma may also be useful for predicting whether hepatic failure is self-limiting.

In summary, relatively preserved attenuation of the liver parenchyma may be a good prognostic factor of TASIT.

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Conflict of interest: The authors have no conflicts of interest to declare or financial associations to disclose.

References
1. Takikawa Y, Endo R, Suzuki K, Fujiwara K, Omata M. Prediction of hepatic encephalopathy development in patients with severe acute hepatitis. Dig Dis Sci 2006; 51: 359-364.
2. Bernuau J, Benhamou J. Fulminant and subfulminant liver failure. In: Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodés J, editors. Oxford textbook of clinical hepatology. Oxford: OXFORD UNIVERSITY press, 1999: 1341-1372.
3. Ware AJ, Cuthbert JA, Shorey J, Gurian LE, Eigenbrodt EH, Combes B. A prospective trial of steroid therapy in severe viral hepatitis. The prognostic significance of bridging necrosis. Gastroenterology 1981; 80: 219-224.
4. Theodossi A, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut 1982; 23: 75-79.
5. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The Acute Hepatic Failure Study Group. Dig Dis Sci 1991; 36: 1223-1228.
6. Ascher NL, Lake JR, Emond JC, Roberts JP. Liver transplantation for fulminant hepatic failure. Arch Surg 1993; 128: 677-682.
7. Kotoh K, Enjoji M, Nakamuta M, Yoshimoto T, Kohjima M, Morizono S, et al. Arterial steroid injection therapy can inhibit the progression of severe acute hepatic failure toward fulminant liver failure. World J Gastroenterol 2006; 12: 6678-6682.
8. Ushijima Y, Tajima T, Yoshimitsu K, Irie H, Nishie A, Hirakawa M, et al. Radiological catheter placement for transcatheter arterial steroid injection therapy to treat severe acute hepatic failure: technical feasibility and efficacy. Acta Radiol 2012; 53: 140-146.
9. Kotoh K, Kato M, Kohjima M, Nakamuta M, Enjoji M. A new treatment strategy for acute liver failure. World J Hepatol 2010; 2: 395-400.
10. Murakami T, Baron R, Peterson M. Liver necrosis and regeneration after fulminant hepatitis: pathologic correlation with CT and MR findings. Radiology 1996; 198: 239-242.
11. Kumahara T, Muto Y, Moriwaki H, Yoshida T, Tomita E. Determination of the integrated CT number of the whole liver in patients with severe hepatitis as an indicator of the functional reserve of the liver. Gastroenterol Jpn 1989; 24: 290-297.
12. Soyer P, Lacheheb D, Levesque M. CT arterial portography of the abdomen: effect of injecting papaverine into the mesenteric artery on hepatic contrast enhancement. Am J Roentgenol 1993; 160: 1213-1215.
13. Tidebrant G, Lukes P, Wihe A. CT attenuation of normal liver parenchyma on delayed scanning with iohexol. Acta Radiol 1992; 33: 502-503.
14. Kakir B, Teksam M, Tarhan NC, Isiklar I, Tutar NU, Ozcan F, et al. Unusual MDCT and sonography findings in fulminant hepatic failure resulting from hepatitis A infection. Am J Roentgenol 2005; 185:1033-1035.
15. Itai Y. CT findings of fulminant hepatitis: terminology and distribution of massive necrosis. Radiology. 1996; 200: 872.
16. Matsui A, Mochida S, Ohno A, Nagoshi S, Hirose T, Fujiwara K. Plasma osteopontin levels in patients with fulminant hepatitis. Hepatol Res 2004; 29: 202-206.
17. Hiraoka A, Horiike N, Akbar SM, Michitaka K, Matsuyama T, Onji M. Soluble CD163 in patients with liver diseases: very high levels of soluble CD163 in patients with fulminant hepatic failure. J Gastroenterol 2005; 40: 52-56.
18. Mitaka A, Hashikura Y, Tagawa Y, Nakayama J, Kawakubo M, Miyagawa S. Expression of Fas ligand by hepatic macrophages in patients with fulminant hepatic failure. Am J Gastroenterol 2005; 100: 2551-2559.
19. Iwaki T, Sugimura M, Nishihira J, Matsuura T, Kobayashi T, Kanayama N. Recombinant adenovirus vector bearing antisense macrophage migration inhibitory factor cDNA prevents acute lipopolysaccharide-induced liver failure in mice. Lab Invest 2003; 83: 561-570.
20. Shakil AO, Jones BC, Lee RG, Federle MP, Fung JJ, Rakela J.
Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci 2000; 45: 334-339.

21. Glaser J, Pausch J. The risk of liver biopsy. Z Gastroenterol. 1995; 33: 673-676.

22. Colapinto RF. Transjugular biopsy of the liver. Clin Gastroenterol.