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ORIGINAL ARTICLE

횡문근융해 시 동반 간질환 유무에 따른 혈청 아미노전달효소치의 차이

조경민, 허내윤, 박승하, 문영수, 김태오, 박종하, 최준혁, 박용은, 이진
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Serum Aminotransferase Level in Rhabdomyolysis according to Concurrent Liver Disease

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Background/Aims: The serum aminotransferase level is usually elevated in rhabdomyolysis, and these enzymes originate from the skeletal muscle. On the other hand, there is limited data showing whether the degree of elevation of these enzymes differs according to the concurrent liver disease.
Methods: Patients with rhabdomyolysis were selected when their serum creatinine kinase level was >1,000 U/L. They were categorized as the group with and without concurrent liver disease. The AST and ALT levels in both groups were compared. In addition, the aminotransferase level was compared between those with rhabdomyolysis and those with alcoholic liver disease.
Results: Among the 165 patients with rhabdomyolysis, 19 had concurrent liver disease. The median peak AST was higher in the group with concurrent liver disease (332 U/L [interquartile range (IQR), 127-1,604] vs. 219 U/L [IQR, 115-504]). In addition, the median peak ALT was higher in the group with concurrent liver disease (107 U/L [IQR, 74-418] vs. 101 U/L [IQR, 56-218]). On the other hand, there was no significant difference in both enzymes between the two groups. The median peak AST level was significantly higher in those with rhabdomyolysis than in those with alcoholic liver disease (221 U/L [IQR, 118-553] vs. 103 U/L [IQR, 59-206]), but the median peak ALT was not significantly different (102 U/L [IQR, 58-222] vs. 51 U/L [IQR, 26-117]).
Conclusions: Rhabdomyolysis showed an elevated AST-dominant aminotransferase level, which is not different according to concurrent liver disease. Therefore, it is recommended that rhabdomyolysis be considered first in cases of elevated aminotransferase levels in patients with a suspicious skeletal muscle injury. **(Korean J Gastroenterol 2019;74:205-211)**

Key Words: Rhabdomyolysis; Aspartate aminotransferases; Alanine transaminase; Liver diseases

INTRODUCTION

Serum aminotransferases, such as AST and ALT, are considered the representative markers for hepatocellular necrosis in acute or chronic hepatitis. When hepatotoxic events occur, the damage to hepatocytes and the increased permeability of hepatocyte cell membrane may contribute to the intravascular spread of these enzymes from hepatocytes, which reflects the current hepatic inflammation. On the other hand, aminotransferase is also present in the skeletal muscle, heart, kidney, brain, and erythrocytes. Hence, the elevated serum aminotransferase level may originate from an extrahepatic organ.[1]

Rhabdomyolysis is a well-known condition, in which a high

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serum aminotransferase level is not a marker for hepatocellular necrosis. Several studies reported that the change in serum AST and ALT is correlated with the serum creatinine kinase (CK) level, which suggests that elevated aminotransferase in rhabdomyolysis might be a marker for a skeletal muscle injury instead of hepatocyte damage.[2-4]

On the other hand, there is limited data on the serum aminotransferase level in rhabdomyolysis in cases of coexistent liver disease. Therefore, this study evaluated the serum aminotransferase level in rhabdomyolysis to determine if concurrent liver disease is present. In addition, the aminotransferase level in rhabdomyolysis and alcoholic liver disease without rhabdomyolysis was compared.

SUBJECTS AND METHODS

1. Study subjects

Rhabdomyolysis was defined as a serum CK level above 1,000 U/L without other causes of elevated CK except for skeletal muscle injury. Two hundred twenty one patients diagnosed with rhabdomyolysis in a Inje University Haeundae Paik Hospital between April 1, 2010 and May 31, 2014 were identified according to the Korean Standard Classification of Diseases (M62.80-89, rhabdomyolysis, specific site and unspecified; N17.9, rhabdomyolysis related to acute renal failure; T79.6, traumatic rhabdomyolysis) on an electronic medical record review. Among them, 165 patients were selected after excluding those in whom the serum CK was <1,000 U/L or unavailable, and those who had other causes of the elevated CK levels, such as acute myocardial infarction, brain hemorrhage, or multi-organ dysfunction (Fig. 1).

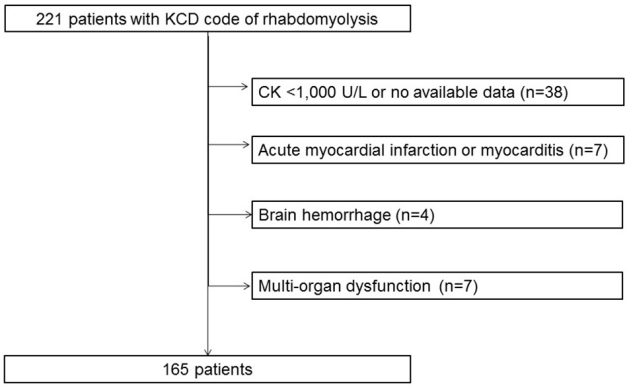

Fig. 1. Flowchart of the enrollment of patients with rhabdomyolysis. KCD, Korean Standard Classification of Diseases; CK, creatinine kinase.

To compare with other diseases with a similar pattern of aminotransferase elevation, 146 patients with the alcoholic liver disease without rhabdomyolysis were selected from those admitted in the same hospital from April 1, 2010 and February 28, 2011. The Institutional Review Board of Inje University Haeundae Paik Hospital approved this study (No. 129792-2013-106). Informed consent was waived because this study was based on a retrospective medical record review.

2. Data collection

The following demographic and laboratory data were collected: the cause of rhabdomyolysis, age, gender, CK, complete blood count, INR, total bilirubin, GGT, LDH, BUN, creatinine, CRP, AST, ALT, and concurrent liver disease at admission and hemodialysis during admission. In addition, the peak level of CK (upper measurement limit, 10,000 U/L), AST, ALT, INR, LDH, BUN, and creatinine during admission were collected.

3. Statistical analysis

Descriptive statistics of the baseline and peak levels of the laboratory findings were obtained from the patients with rhabdomyolysis. The clinical data, including CK, AST, ALT, and AST/ALT ratio at the peak AST time, were compared according to the presence of concurrent liver disease. The same clinical data between the patients with rhabdomyolysis and those with the alcoholic liver disease without rhabdomyolysis were also compared. The categorical variables were assessed using a chi-square test or Fisher's exact test. Continuous variables were assessed by Student's t-test. A p-value <0.05 was considered significant. Statistical analyses were performed using SPSS, version 25.0 (SPSS Inc., Chicago, IL, USA) and R (version 3.5.3; available from: http://cran.r-project.org/).

RESULTS

1. Cause of rhabdomyolysis

Direct muscle injury, non-traumatic exertional causes, non-traumatic non-exertional causes, and unknown causes were noted in 28 (17%), 38 (23%), 94 (57%), and five (3%) patients, respectively. Direct muscle injury included burn, trauma, postoperative injury, and compression. Non-traumatic exertional causes included extreme muscle movement. Non-traumatic non-exertional causes included immobilization for a range

of reasons, seizure, sepsis, etc. (Table 1 and Fig. 2).

2. Baseline characteristics of the patients with rhabdomyolysis

The mean age of the patients was 51.8 years, and the male gender was predominant (63.6%). The initial CK level was 4,032 U/L, and mild leukocytosis and CRP elevation were observed. The initial AST and ALT levels were 121 and 52 U/L, respectively. Among them, 19 patients had concurrent liver disease; HBV in four, HCV in one, alcohol in 13, and drug-induced liver injury (culprit drug: simvastatin) in one (Table 2).

3. Peak laboratory findings during admission

During admission, the peak CK level and peak LDH level were 8,780 U/L (range, 1,016-10,000), and 640 U/L (IQR, 427-1,084), respectively. The peak AST level and ALT level were 221 U/L (IQR, 118-553) and 102 U/L (IQR, 58-222), respectively. The median value of the AST/ALT ratio at the peak AST time was 2.5. The proportion of peak AST over the

Table 1. Cause of Rhabdomyolysis

Cause	Number of patients
Direct muscle injury	28
Burn	11
Trauma	10
Postoperative injury	5
Compression	2
Non-traumatic exertional cause	38
Extreme muscle movement	31
Heat stroke	4
Long-standing	1
Overworking	1
Hyperactivity	1
Non-traumatic non-exertional cause	94
Immobilization	21
Seizure	20
Sepsis	7
Non-specific enteritis	6
Pneumonia	6
Viral meningitis/encephalitis	6
Drug	5
Upper respiratory infection	4
Hypoglycemia	3
Vibrio myositis	2
Snake bite	2
Cardiac arrest	2
Hypokalemia	2
Rupture of pheochromocytoma	1
Diabetic ketoacidosis	1
Toxic hepatitis	1
Herb	1
Cellulitis	1
Herpes zoster	1
Ureter stone	1
Tetanus	1
Unknown	5

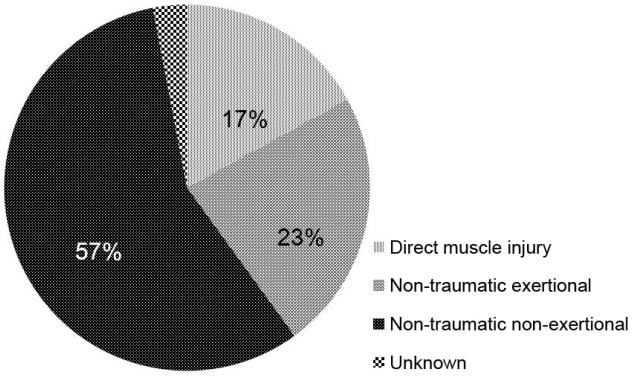

Fig. 2. Cause of rhabdomyolysis.

Table 2. Baseline Characteristics of Patients with Rhabdomyolysis during Admission

Variable	Value (n=165)
Age[a] (years)	51.8±20.0
Male	105 (63.6)
Creatinine kinase[b] (U/L)	4,032 (26-10,000)
White blood cell count[c] (/mm^3)	10,380 (7,295-14,940)
Hemoglobin[c] (g/dL)	13.6 (12.0-15.5)
Platelet count[c] (×10^3/mm^3)	203 (154-243)
INR[c]	1.06 (1.00-1.15)
Total bilirubin[c] (mg/dL)	0.7 (0.5-1.0)
Gamma glutamyl transferase[c] (U/L)	29 (17-73)
Lactate dehydrogenase[c] (U/L)	426 (313-730)
Blood urea nitrogen[c] (mg/dL)	17.0 (12.1-26.5)
Creatinine[c] (mg/dL)	1.1 (0.9-1.6)
C-reactive protein[c] (mg/dL)	1.26 (0.18-5.43)
AST[c] (U/L)	121 (49-298)
ALT[c] (U/L)	52 (28-119)
Concurrent liver disease	19 (11.5)

The upper limit of measurement of creatinine kinase was 10,000 U/L. INR, international normalization ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]This value is a mean±standard deviation; [b]This value is a median (range); [c]This value is a median (interquartile range).

upper limit of normal (38 U/L) was 97.8%, and that of the peak ALT over the upper limit of normal (43 U/L) was 84.1% (Fig. 3 and Table 3).

4. Clinical and laboratory findings in patients with rhabdomyolysis according to concurrent liver disease

The mean age of the patients was 51.4±20.8 years and 54.6±11.6 years in the group with and without concurrent liver disease, respectively (p=0.33). Both groups showed a male predominance. Only one of the rhabdomyolysis patients had cirrhosis, but more than 60% of the alcoholic liver disease patients had cirrhosis. The peak CK level was similar in the two groups. The peak AST level was higher in the group with concurrent liver disease (332 U/L [IQR, 127-1,604] vs. 219 U/L [IQR, 115-504]). In addition, peak ALT level was higher in the group with concurrent liver disease (107 U/L [IQR, 74-418] vs. 101 U/L [IQR, 56-218]). The AST/ALT ratio at the median value of the peak AST time was higher in the group with concurrent liver disease (3.5 vs. 2.5). On the other hand, all the values were similar in both groups (Table 4).

5. Clinical and laboratory findings in patients with rhabdomyolysis and alcoholic liver disease without rhabdomyolysis

Compared to the patients who were admitted due to alco-

Table 3. Peak Laboratory Findings of Patients with Rhabdomyolysis during Admission

Variable	Value (n=165)
Peak creatinine kinase[a] (U/L)	8,780 (1,016-10,000)
Peak prothrombin time INR[b]	1.10 (1.02-1.27)
Peak total bilirubin[b] (mg/dL)	1.0 (0.7-1.5)
Peak lactate dehydrogenase[b] (U/L)	640 (427-1,084)
Peak AST[b] (U/L)	221 (118-553)
Peak ALT[b] (U/L)	102 (58-222)
AST/ALT ratio at peak AST time[b]	2.5 (1.8-3.4)
Peak BUN[b] (mg/dL)	19.7 (13.9-36.0)
Peak creatinine[b] (mg/dL)	1.2 (0.9-2.1)
Peak total bilirubin[b] (mg/dL)	1.0 (0.7-1.5)
Peak INR[b]	1.10 (1.02-1.27)
Hemodialysis	11 (6.7)

The upper limit of measurement of creatinine kinase was 10,000 U/L.
INR, international normalization ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.
[a]This value is a median (range); [b]This value is a median (interquartile range).

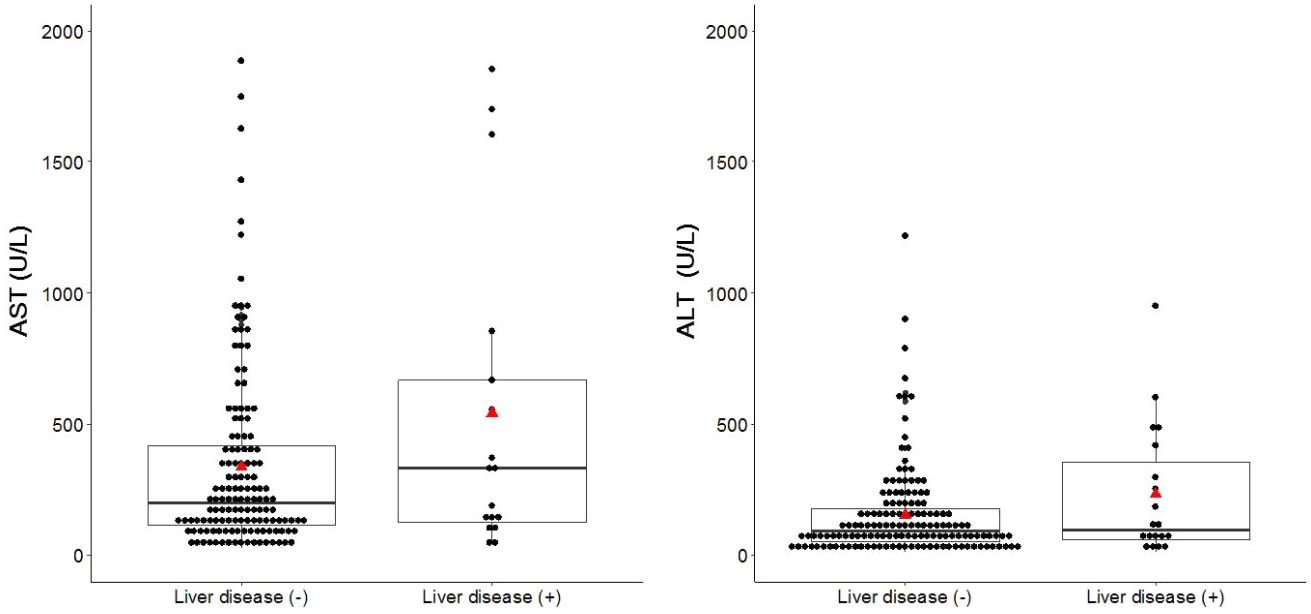

Fig. 3. Distribution of serum AST and ALT in the patients with rhabdomyolysis according to the presence of liver disease. Seven and two outliers of serum AST over 2,000 U/L in the patients with or without liver disease were omitted, respectively. Two outliers of serum ALT over 2,000 U/L in those without liver disease were omitted in this graph. The mean and median value of each variable was described as a red triangle and black thick horizontal bar in the box respectively. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

holic liver disease without rhabdomyolysis, those with rhabdomyolysis showed a significantly higher white blood cell count, hemoglobin, platelet count, and CK level. The peak AST level was significantly higher in those with rhabdomyolysis than in those with alcoholic liver disease (221 U/L [IQR, 118-553] vs. 103 U/L [IQR, 59-206]). On the other hand, the peak ALT level was similar in both groups (102 U/L [IQR, 58-222] vs. 51 U/L [26-117]). The AST/ALT ratio at the peak AST time was higher in those with rhabdomyolysis than in those with alcoholic liver disease (3.4 vs. 2.5) but without statistical significance (Table 5).

DISCUSSION

This study showed that the serum aminotransferase level was not significantly different in patients with rhabdomyolysis regardless of concurrent liver disease. In addition, the peak AST level was higher in those with rhabdomyolysis than in alcoholic liver disease, but the AST/ALT ratio could not distinguish the two diseases effectively.

Table 4. Clinical and Laboratory Findings in Patients with Rhabdomyolysis according to Concurrent Liver Disease

Group	Concurrent liver disease[a] (n=19)	No concurrent liver disease (n=146)	p-value
Age[b] (years)	54.6±11.6	51.4±20.8	0.33
Male	15 (78.9)	90 (61.6)	0.21
Initial creatinine kinase[c] (U/L)	3,038 (149-10,000)	4,173 (26-10,000)	0.51
Peak creatinine kinase[c] (U/L)	10,000 (2,244-10,000)	8,380 (1,016-10,000)	0.20
Peak lactate dehydrogenase[d] (U/L)	1,054 (467-2,131)	632 (425-971)	0.13
Peak AST[d] (U/L)	332 (127-1,604)	219 (115-504)	0.19
Peak ALT[d] (U/L)	107 (74-418)	101 (56-218)	0.64
AST/ALT ratio at peak AST time[d]	3.4 (1.8-5.1)	2.5 (1.8-3.3)	0.10
Peak total bilirubin[d] (mg/dL)	1.6 (1.0-3.5)	0.9 (0.6-1.3)	0.40
Peak INR[d]	1.1 (1.0-1.3)	1.1 (1.0-1.3)	0.31
Peak creatinine[d]	1.17 (0.98-3.67)	1.17 (0.93-2.14)	0.43
Hemodialysis	2 (10.5)	9 (6.2)	0.62

AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalization ratio.
[a]This included viral hepatitis B or C, alcoholic liver disease, and drug-induced liver liver injury; [b]This value is a mean±standard deviation; [c]This value is a median (range); [d]This value is a median (interquartile range).

Table 5. Clinical and Laboratory Findings in Patients with Rhabdomyolysis and Alcoholic Liver Disease without Rhabdomyolysis

Group	Rhabdomyolysis (n=165)	Alcoholic liver disease without RM (n=146)	p-value
Age[a] (years)	51.8±20.0	54.6±11.6	0.12
Male	105 (63.6)	129 (88.4)	<0.01
Liver cirrhosis	1 (0.6)	91 (62.3)	<0.01
White blood cell count[b] (/mm^3)	10,380 (7,295-14,940)	7,880 (5,480-10,880)	<0.01
Hemoglobin[b] (g/dL)	13.8 (12.0-15.5)	12.0 (9.7-13.9)	<0.01
Platelet count[b] (×10^3/mm^3)	203 (154-243)	127 (84-183)	<0.01
Peak creatinine kinase[c]	8,780 (1,016-10,000)	131 (10-993)	<0.01
Peak AST[b] (U/L)	221 (118-553)	103 (59-206)	0.02
Peak ALT[b] (U/L)	102 (58-222)	51 (26-117)	0.24
AST/ALT ratio at peak AST time[b]	2.5 (1.8-3.4)	2.3 (1.6-3.3)	0.81
Peak total bilirubin[b] (mg/dL)	1.0 (0.7-1.5)	2.3 (1.2-4.8)	<0.01
Peak INR[b]	1.10 (1.02-1.27)	1.33 (1.08-1.62)	0.18
Peak creatinine[b]	1.17 (0.94-2.14)	1.00 (0.84-1.29)	<0.01

RM, rhabdomyolysis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalization ratio.
[a]This value is a mean±standard deviation; [b]This value is a median (range); [c]This value is a median (interquartile range).

For a long time, the serum aminotransferase activity has been included in the liver function test, where it could indicate hepatocellular necrosis. In hepatocytes, AST is located in the cytosol and mitochondria, whereas ALT is found only in the cytosol.[1] When the various hepatotoxic events caused by viruses, alcohol, drugs, and toxins produce hepatic inflammation, AST and ALT are released through the disrupted or permeable cell membrane from the hepatocytes. On the other hand, the specificity of aminotransferase for hepatic inflammation is low because these enzymes are present in a variety of organs outside of the liver, and an injury to another organ may produce a similar elevation of serum aminotransferase. In particular, AST is located in the liver, skeletal muscle, heart, kidneys, pancreas, and erythrocytes; thus, both hepatic inflammation and an injury to another organ should be considered when the serum AST level is elevated.[1]

Rhabdomyolysis is one of the representative conditions, in which serum aminotransferase is elevated without significant liver disease, and AST is usually higher than ALT. According to another study, the serum peak AST level was correlated with the peak CK, and the serial test result during admission showed a similar pattern between both enzymes.[2,4] These findings suggest that an elevated AST level in rhabdomyolysis might be a marker of skeletal muscle injury instead of hepatocyte damage. In the present study, serum peak AST elevation was approximately five times the upper limit of normal, and the peak ALT elevation was more than two times the upper limit of normal, which concurs with a previous study.[4] An elevated AST level is intuitively explainable because AST is one of the sarcoplasmic proteins. On the other hand, ALT is usually accepted as a more specific marker for hepatocyte injury. Nevertheless, a study reported that there is evidence of ALT production outside of the liver. For example, the skeletal muscle, heart, and kidneys contained 10%, 15%, and 40% of the ALT concentration found in the liver, respectively.[5] Therefore, ALT elevation is also possible in the case of a skeletal muscle injury without liver damage.

Initially, this study examined whether the serum aminotransferase level is higher in the group with rhabdomyolysis and concurrent liver disease than in those with only rhabdomyolysis. In the present study, the AST and ALT levels were similar in the two groups, but the AST level was slightly higher in the group with rhabdomyolysis and concurrent liver disease. Most of the patients with chronic viral hepatitis were assumed to be in the inactive phase of the disease except for one case. The index case was a 65-year-old woman without previous chronic liver disease. Her CK level was >10,000 U/L, AST 1,854 U/L, and ALT level 486 U/L, and she had a high serum HBV DNA level. Initial sonography revealed increased periportal echogenicity. Two months later, her CK levels were normalized, but she complained of persistent fatigue. Her serum aminotransferase levels were mildly elevated (AST, 75 U/L; ALT, 48 U/L), and her HBV DNA level was 7.0×10^6 IU/mL. Liver CT revealed a shrunken liver and a large amount of ascites. Consequently, the nucleoside analog, entecavir was administered. Nine months later, her AST and ALT levels were normalized; her ascites disappeared and a complete virologic response for HBV was accomplished (Fig. 4). This case suggests that it is still necessary to work up the possible cause of hepatitis in the setting of an elevated aminotransferase level in rhabdomyolysis.

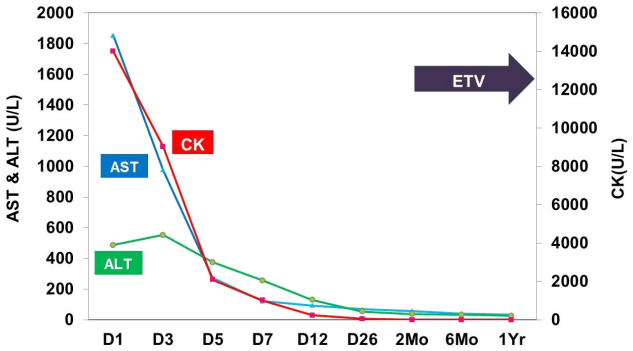

Fig. 4. Laboratory findings over time in the index case with rhabdomyolysis and hepatitis B virus infection. AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; ETV, entecavir; D, day; Mo, month; Yr, year.

The AST/ALT ratio is helpful for differentiating the kind of acute or chronic liver disease. In acute viral hepatitis, the AST/ALT ratio is generally less than one. In contrast, the AST/ALT ratio is usually more than one in alcoholic hepatitis or cirrhosis. In particular, alcoholic hepatitis presents with AST/ALT ratios >2-3.[6,7] Therefore, this study compared the aminotransferase and AST/ALT ratio in those with rhabdomyolysis and those with the alcoholic liver disease without muscle injury. The AST and ALT levels were higher in the rhabdomyolysis group, but without statistical significance. The AST/ALT ratio was approximately 2.5 in both groups. Hence, it might not be helpful for discriminating between the two groups.

This study has some limitations. First, in the case of sepsis, some patients might experience hypotension, which could in-

duce an ischemic hepatic injury. Thus, it is impossible to discriminate the cause of the elevated aminotransferase between rhabdomyolysis and ischemic hepatic injury precisely. To minimize the controversial cases, multi-organ failure, which might be associated with septic shock, was excluded. Second, this was a type of cross-sectional study to describe an episode of rhabdomyolysis. Therefore, it is difficult to present the causality or relationship between the elevated aminotransferase and rhabdomyolysis directly. Most patients had an initial routine viral hepatitis serology but an examination of the rare causes of acute or chronic hepatitis was not performed. Nevertheless, the physicians tried to refer to hepatology in suspicious cases of chronic liver disease after discharge. In addition, except one index case of chronic viral hepatitis, no one showed an aggravation of the liver function. Third, the alcoholic liver disease group did not include the pure aggravated liver function case due to alcohol intake exclusively. Owing to the high proportion of cirrhosis cases, some patients were admitted due to variceal bleeding, encephalopathy, and systemic infection. Thus, this cohort might not present with a higher AST/ALT ratio as expected in pure alcoholic hepatitis. Finally, the number of patients with rhabdomyolysis and concurrent liver disease was too small, which may have affected the statistical reliability to compare the variables between the rhabdomyolysis alone group and rhabdomyolysis with liver disease group.

In conclusion, patients with rhabdomyolysis showed elevated aminotransferase levels, both AST and ALT. The degree of the elevation was similar in the patients with and without concurrent liver disease. The AST/ALT ratio in rhabdomyolysis increased in a similar manner to those with alcoholic liver disease. Therefore, it is important to consider rhabdomyolysis in a differential diagnosis in cases of an elevated AST-dominant aminotransferase level in patients with a suspicious skeletal muscle injury.

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