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Abstract

Of the eight patients with fulminant hepatitis placed under total parenteral nutrition with an amino acid solution rich in branched chain amino acids and treated by plasma exchange, four survived and four died from hepatic failure. Serum uric acid levels in the non-survived group were significantly lower on days 1-6 compared with the survived group. The concentration ratios of uric acid to creatinine and prothrombin time were significantly lower on days 5-8 and days 3-8, respectively, in a similar comparison. Thus, the uric acid to creatinine ratio, which corrects for the possible renal dysfunction associated with acute hepatic failure, may serve as a clinically useful prognostic indicator for patients with fulminant hepatitis.

KEYWORDS: fulminant hepatitis, uric acied, hypouricemia, uric acied/creatinine ratio

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Evaluation of Serum Uric Acid to Creatinine Ratio in Fulminant Hepatitis

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Of the eight patients with fulminant hepatitis placed under total parenteral nutrition with an amino acid solution rich in branched chain amino acids and treated by plasma exchange, four survived and four died from hepatic failure. Serum uric acid levels in the non-survived group were significantly lower on days 1-6 compared with the survived group. The concentration ratios of uric acid to creatinine and prothrombin time were significantly lower on days 5-8 and days 3-8, respectively, in a similar comparison. Thus, the uric acid to creatinine ratio, which corrects for the possible renal dysfunction associated with acute hepatic failure, may serve as a clinically useful prognostic indicator for patients with fulminant hepatitis.

Key words: fulminant hepatitis, uric acid, hypouricemia, uric acid/creatinine ratio

Fulminant hepatitis is a relatively rare but mostly fatal condition associated with viral hepatitis and drug-induced liver damage. Early assessment of critically impaired liver function is the crucial to improve the prognosis of patients with this disease and also to select the most effective and appropriate treatments.

To evaluate the residual liver function in fulminant hepatitis, we utilize not only hemato-biochemical liver function tests, *e.g.*, prothrombin time, arterial ketone body ratio, and indocyanine green disappearance rate, but also imaging modalities, *e.g.*, computed tomography, asialoglycoprotein receptor-scintigram and ultrasonography. However, these tests are not necessarily available at all times in cases of severe liver failure because of problems related to the complexity, reproducibility, rapidity, and cost performance of these tests.

Hypouricemia has been reported in cases of acute hepatitis and acute liver failure although its relation to the assessment of prognosis was not investigated (1-3). Since the liver is the central organ of uric acid metabolism, we investigated the utility of serum uric acid level as an indicator of the residual liver function by correcting with creatinine due to the possible involvement of renal dysfunction, which is frequently present in fulminant hepatitic failure. The concentration ratio of serum uric acid to creatinine (UA/CR) was analyzed in the present study in eight patients with fulminant hepatitis as defined by Ichida *et al.* (4) for the evaluation of critically impaired residual liver function in acute liver failure.

Subjects and Methods

Patients. Eight patients with fulminant hepatitis (4) admitted to Okayama University Hospital between 1988 and 1993 were included in this study. The inclusion criteria were: (i) no major complications which may prevent the cessation of liver support, (ii) treatment only by plasma exchanges with 3,200 ml of fresh frozen plasma per day for 6 consecutive days from admission, and (iii) follow-up with a complete set of data given below.

Of the eight patients, four survived (2 cases of fulminant hepatitis, acute form; 2 cases of fulminant hepatitis, subacute form; and 3 women and 1 man) and four died (2 cases of fulminant hepatitis, acute form; 2 cases of fulminant hepatitis, subacute form; and 2 women and 2 men). The causes of the death were all hepatic failure. The clinical background of the patients with other laboratory data are given in Table 1.

Study protocol. All patients were maintained by total parenteral nutrition (TPN) with a commercially available amino acids solution rich in branched chain amino acids. Plasma exchange was performed with 3,200 ml of fresh frozen plasma every time and venous blood samples were taken approximately 20 h after plasma exchange. UA/CR ratios were monitored together with

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Table I Clinical background of patients with fulminant hepatitis

	Case	Age	Sex	Etiology	Clinical course (died on)	T-Bil(mg/dl)	GPT(IU/l)	CR(mg/dl)
Non-survived								
	1	32	F	HBV	Acute (day 11)	18.4	229	0.47
	2	29	F	NANBV	Acute (day 14)	13.5	368	0.49
	3	49	M	HBV	Subacute (day 8)	22.6	569	0.73
	4	57	F	NANBV	Subacute (day 22)	29.5	394	0.46
Survived								
	5	18	M	HAV	Acute	6.76	777	2.14
	6	56	F	HBV	Subacute	10.7	314	0.93
	7	25	F	NANBV	Subacute	9.55	83	0.47
	8	24	F	HBV	Acute	7.96	1806	7.70

T-Bil, total bilirubin; CR, creatinine; F, female; M, male; HBV, hepatitis B virus; NANBV, non-A non-B hepatitis virus; HAV, hepatitis A virus. The results of liver function tests were those determined on admission.

other parameters during the course of admission for a maximum of 14 hospital days, this time limit being chosen to obtain a maximum number of survived and non-survived cases. Day 0 was the day plasma exchange was initiated, so that day 1 marks a 24 period after the first plasma exchange.

All biochemical tests were carried out using an autoanalyser (HITACHI 736, Japan). Serum uric acid was assayed by the uricase-peroxidase method (5), and serum creatinine by the creatininase-creatinase-sarcosin oxidase-peroxidase method (6). Prothrombin time was expressed as percent of normal prothrombin activity. Statistical significance of differences was analyzed by the Mann-Whitney U-test and P values below 0.05 were considered significant.

Results

The clinical background of the eight patients with fulminant hepatitis is given in Table 1. Serum bilirubin levels determined at the time of admission were higher in the four non-survived patients than in a group of survived patients, although GPT did not separate the two groups. Serum creatinine level was increased in two of the survived patients, indicating the presence of renal dysfunction. Clinical courses of 8 patients are given in Figs. 1 and 2. Non-survived patients (cases 1 to 4) generally had low serum levels of uric acid with slight elevations in terminal stages. Serum creatinine showed similar changes. When the serum uric acid level was corrected by serum creatinine concentration, the resulting UA/CR ratios were consistently low, mostly below 3.0, with or without terminal rises in these fatal cases. The UA/CR ratio roughly correlated with prothrombin time, and also with the grade of hepatic coma. On the other hand, in survived patients, serum uric acid levels were generally higher than those of fatal cases, and fluctuated considerably with time. Serum creatinine showed similar changes in some cases, particularly in case 8, who had HBV nephropathy in early hospital days. When the uric acid levels of these patients were corrected by creatinine, the UA/CR ratios were generally higher than those of fatal patients and mostly above 3.0. The ratio appeared to be correlated with the clinical course as represented by the prothrombin time, and in cases with low initial ratios, they tended to increase as the clinical course improved. In case 8 who had HBV nephropathy, her UA/CR ratio remained relatively low while the serum creatinine level stayed above 5.0 mg/dl.

The differences in these parameters between the survived and non-survived groups were analyzed and the results are given in Table 2. Serum uric acid levels in the survived group were significantly higher than in the non-survived group on days 1-2, 3-4 and 5-6. When the uric acid level was corrected by creatinine, the resulting UA/CR ratios in the survived group were significantly higher than in the non-survived group on days 5-6 and 7-8. Prothrombin time values in the survived group were

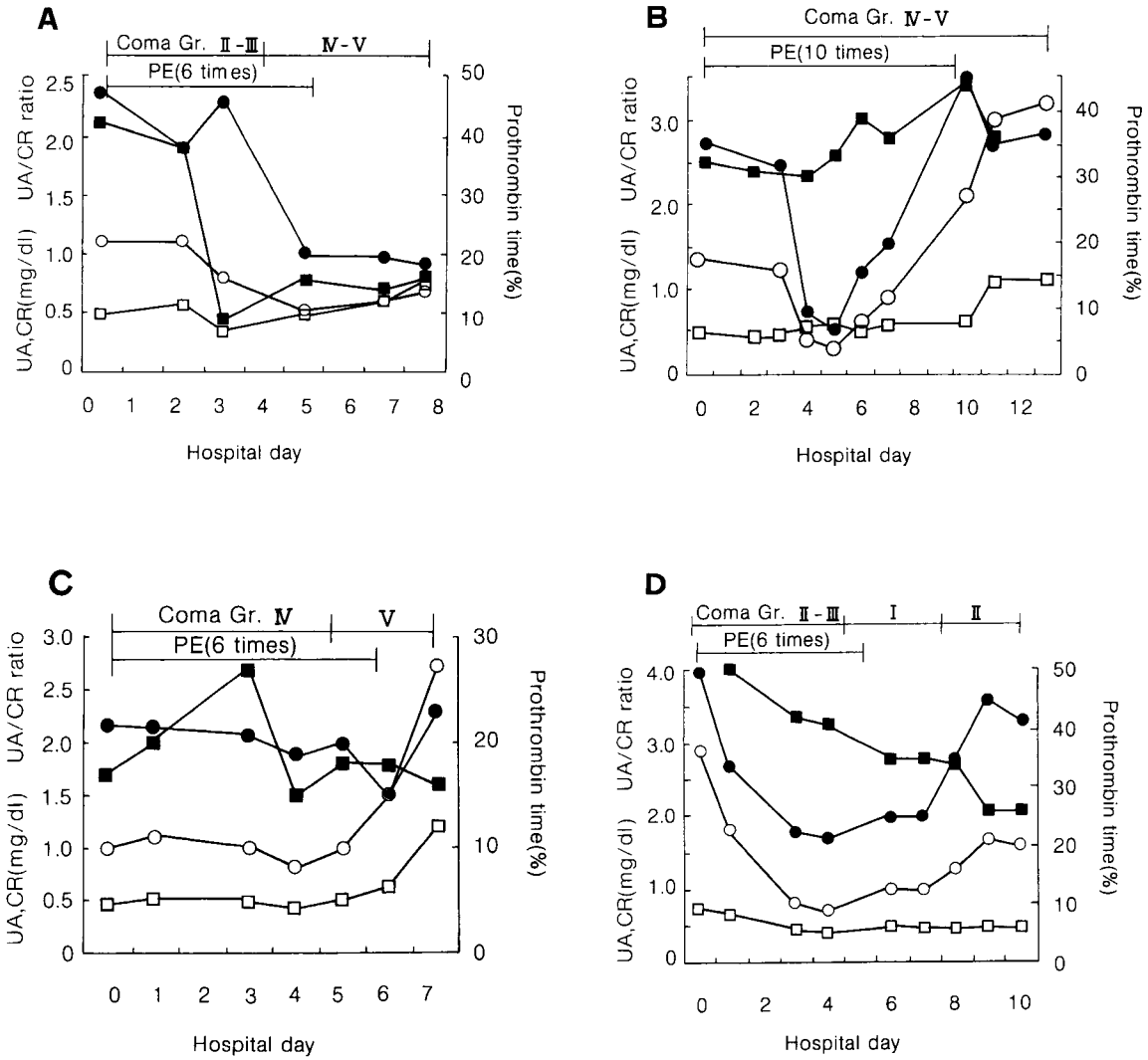

Fig. 1 Clinical course of a non-survived patient with fulminant hepatitis. **A**: Case 1; **B**: Case 2; **C**: Case 3; and **D**: Case 4. ●—●, uric acid/creatine (UA/CR) ratio; ○—○, Uric acid (UA); □—□, Creatinine (CR); and ■—■, Prothrombin time Gr., grade of hepatic encephalopathy; and PE, plasma exchange.

Table 2 Mean values of uric acid/creatinine (UA/CR) ratio, UA, CR, prothrombin time and total bilirubin in survived and non-survived groups of fulminant hepatitis and the significance level in difference between the two groups

Hospital days	UA/CR		UA (mg/dl)		CR (mg/dl)		Prothrombin time (%)		Total bilirubin (mg/dl)	
	S	NS	S	NS	S	NS	S	NS	S	NS
0	2.6	2.7	6.25	1.55	2.81	0.54	40	35	8.8	20.1*
1～2	2.9	2.3	5.65	1.30*	2.70	0.56	50	33	7.3	17.3*
3～4	2.7	1.6	4.93	0.68*	2.66	0.45	69	27*	6.4	20.9*
5～6	3.1	1.4*	4.98	0.90*	2.23	0.50	69	27*	6.8	22.0*
7～8	3.3	1.7*	4.58	1.15	0.87	0.75	67	26*	6.1	26.8*

S, survived group; NS, non-survived group; * $P < 0.05$

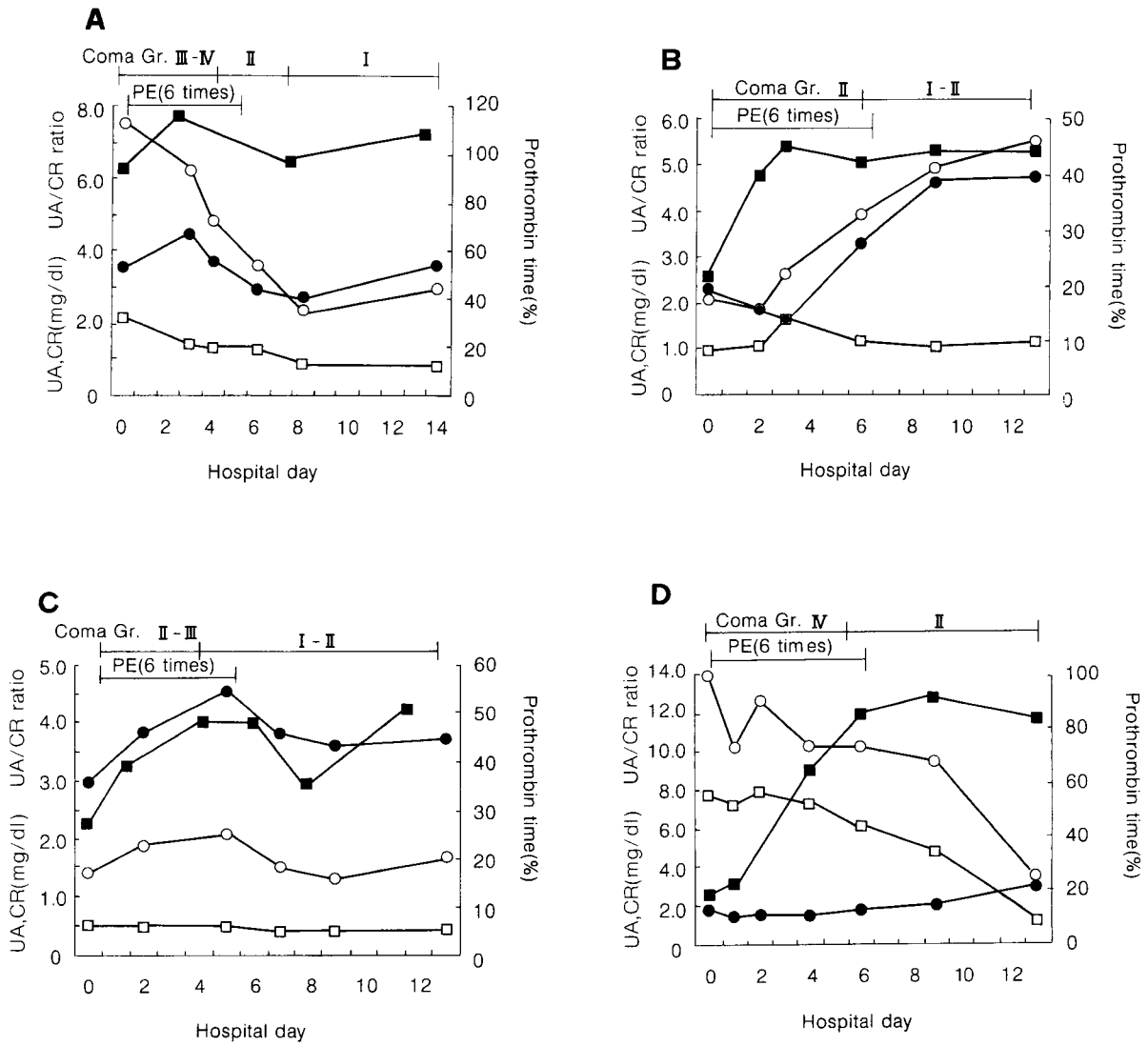

Fig. 2 Clinical course of a survived patient with fulminant hepatitis. **A**: Case 5; **B**: Case 6; **C**: Case 7; **D**: Case 8. The patient had HBV nephropathy, which was reflected by marked rises in serum creatinine and uric acid. Symbols and abbreviations: See the legend to Fig. 1.

similarly higher than in the non-survived group on days 3-4, 5-6 and 7-8. Incidentally, serum bilirubin levels in the non-survived patients were higher than in the survived patients throughout the clinical course given in Table 2.

Discussion

Hypouricemia has been reported in 1% of patients with various diseases (7-13) associated with medication, transfusion, neoplasms, diabetes mellitus and liver injury (14). One of the factors considered to reduce the serum uric acid level in liver injury is hyperexcretion of uric acid into urine in cases of advanced liver injury such as liver cirrhosis with hyperbilirubinemia or metastatic liver tumors (8-9, 15-21). This is related to the reduction of uric acid binding to protein or decreased production of a metabolite that enhances reabsorption of uric acid in the renal tubules (8, 20). Other factors that reduce serum uric acid include decreased *de novo* synthesis of uric acid resulting from hepatocyte dysfunction (20) and semi-starvation state (20). On the contrary, there is a report of increased serum uric acid, probably the result of damaged

liver tissue (1). There are basic studies of purine metabolism (22) which were conducted to evaluate the residual liver function. However, there are few clinical studies on serum uric acid levels in severe liver injury like fulminant hepatitis (2, 3). This is probably because of the difficulty in obtaining survived and non-survived patients with comparable clinical courses, and this difficulty is the main reason the present study population is so small. Because of the importance of evaluating uric acid metabolism in acute hepatic failure, the present study was undertaken, in spite of the small number of patients with fulminant hepatitis in the survived and non-survived groups.

The non-survived patients with fulminant hepatitis in this study not only had increased levels of total bilirubin and lower values of prothrombin time but also lower uric acid levels and lower UA/CR ratios compared with the survived patients. Although serum uric acid levels were lower in fatal cases in this study, uric acid *per se* would not be a suitable prognostic indicator because the plasma uric acid level might be increased in patients complicated by renal dysfunction. When the uric acid level was corrected for possible renal failure with creatinine, there was still a significant difference in the resulting UA/CR ratio between the non-survived and survived groups on days 5-6 and days 7-8. These results are similar to those of prothrombin time, an established marker of severe liver injury. Although serum bilirubin levels in non-survived cases were incidentally all higher than those in survived cases, the total bilirubin level is not generally accepted as an absolute prognostic marker of fulminant hepatitis. The UA/CR ratio of all fatal patients was below 3.0 on days 5-8. Thus, 3.0 could be used as a cut-off when evaluating the prognosis of such cases.

With regard to nutritional status, which is another important regulating factor of serum uric acid level, all patients were placed under TPN, and it was unlikely that the TPN contributed to the reduced uric acid level in the fatal cases mentioned above. It is true that an extrinsic supply of uric acid source derived from foods was deficient in those patients with hepatic failure, but a large amount of fresh frozen plasma given in plasma exchange should have supplied uric acid and its precursors instead. Although hypouricemia under the condition of TPN has been reported (23-28), another report on severe trauma patients indicated that glucose infusion alone may be sufficient to counteract the catabolism induced by trauma in the early phase of injury (29). Therefore, the decrease of serum uric acid level can not be explained simply by fasting. Serum protein level and cholesterol level were not linearly correlated with hypouricemia and with the UA/CR ratio in our patients (data not shown). Thus, the lower UA/CR ratio in patients with fatal fulminant hepatitis could be best explained by impaired uric acid formation as a result of severe hepatic dysfunction.

In conclusion, the UA/CR ratio appears to be a useful parameter to evaluate the residual liver function in patients with fulminant hepatitis because of its simplicity, rapidity, good reproducibility and low cost performance.

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